



(12) **DEMANDE DE BREVET CANADIEN**
CANADIAN PATENT APPLICATION

(13) **A1**

(86) **Date de dépôt PCT/PCT Filing Date:** 2022/06/20
(87) **Date publication PCT/PCT Publication Date:** 2022/12/22
(85) **Entrée phase nationale/National Entry:** 2023/12/14
(86) **N° demande PCT/PCT Application No.:** US 2022/034189
(87) **N° publication PCT/PCT Publication No.:** 2022/266540
(30) **Priorité/Priority:** 2021/06/18 (US63/212,414)

(51) **Cl.Int./Int.Cl.** **C07K 16/18** (2006.01),
A61P 25/00 (2006.01)
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(54) **Titre : ANTICORPS QUI SE LIENT AU DOMAINE γ C DE LA FIBRINE OU DU FIBRINOGENE HUMAIN ET METHODES D'UTILISATION**

(54) **Title: ANTIBODIES WHICH BIND HUMAN FIBRIN OR FIBRINOGEN γ C DOMAIN AND METHODS OF USE**

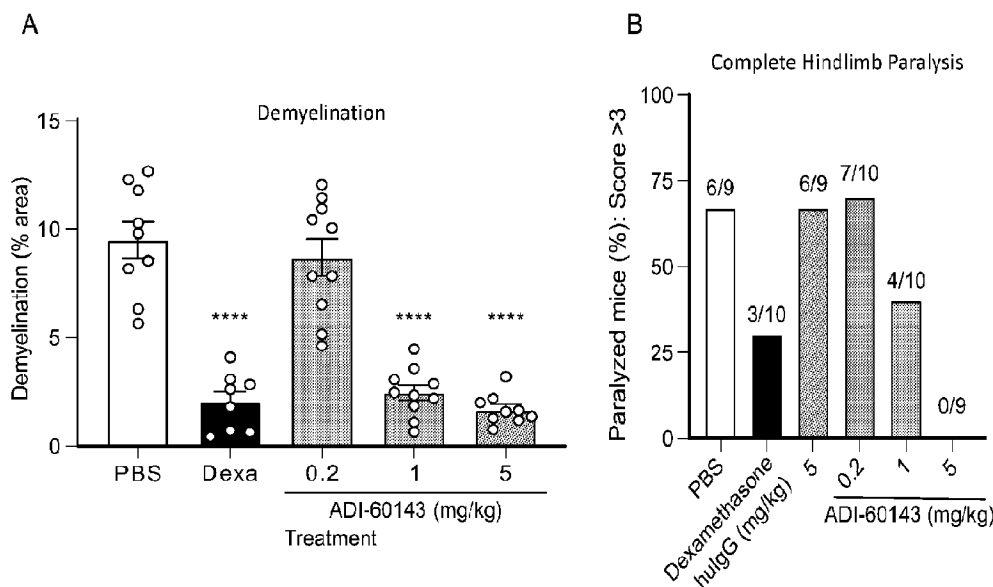


Figure 24

(57) **Abrégé/Abstract:**

Described herein are novel and improved antibodies that bind human fibrin or fibrinogen γ C domain and methods of use thereof. In certain aspects, described herein are methods of inhibiting microglial activation. In certain aspects, described herein are pharmaceutical compositions comprising the antibodies that bind fibrin or fibrinogen γ C domain. In certain aspects, the antibodies and methods described herein are used for treatment of degenerative neuronal disorders that involve inflammatory demyelination.

Date Submitted: 2023/12/14

CA App. No.: 3222880

Abstract:

Described herein are novel and improved antibodies that bind human fibrin or fibrinogen C domain and methods of use thereof. In certain aspects, described herein are methods of inhibiting microglial activation. In certain aspects, described herein are pharmaceutical compositions comprising the antibodies that bind fibrin or fibrinogen C domain. In certain aspects, the antibodies and methods described herein are used for treatment of degenerative neuronal disorders that involve inflammatory demyelination.

Antibodies Which Bind Human Fibrin or Fibrinogen γ C Domain and Methods of Use**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of U.S. Provisional Application No. 63/212,414, filed June 18, 2021, which is hereby incorporated in its entirety by reference.

SEQUENCE LISTING

[0002] Not applicable.

BACKGROUND

[0003] Degenerative neuronal disorders such as multiple sclerosis (MS) can involve inflammatory demyelination and autoimmune responses. Microglia, in particular perivascular microglia, are believed to be necessary not only for the maintenance, but also for the onset of inflammatory demyelination in central nervous system (CNS) autoimmune disease. Activation of microglia contributes to both neuronal and oligodendrocyte death via release of cytokines and nitric oxide. In MS, inflammatory processes are associated with destruction of myelin sheaths, and can also involve axonal damage that can lead to permanent functional deficits, such as paralysis and loss of vision. Resident microglia are responsible for demyelination, via their ability to phagocytose myelin and secrete proinflammatory cytokines.

[0004] In MS lesions, perivascular activation of microglia colocalizes with areas of blood brain barrier (BBB) disruption, and in vivo imaging studies have shown that BBB disruption provokes the immediate and focal activation of microglia. One of the earliest events coupled to BBB disruption in MS is leakage of the blood protein fibrinogen in the nervous system that results in perivascular deposition of fibrin. Fibrinogen is not present in the healthy CNS, but only leaks in the brain after BBB disruption, thus serving as an environmental "danger" signal. Upon conversion of fibrinogen to fibrin, the CD11b/CD18 integrin receptor (also referred to as: Mac-1, α Mf1 2, Complement Receptor 3) binds to the fibrin and induces microglial activation leading to inflammatory demyelination. CD11b is the alpha chain of the receptor that regulates phagocytosis of myelin during inflammatory demyelination. Immobilized fibrinogen and insoluble fibrin, but not soluble fibrinogen, have been identified as physiological, high-affinity ligands for Mac-1.

[0005] The γ 377-395 epitope of the fibrin or fibrinogen γ C domain is the binding epitope of fibrin to CD11b. The fibrin $\gamma^{377-395}$ peptide functions as an inhibitor of microglia activation by blocking fibrin binding to Mac-1. Because fibrin mediates blood coagulation by binding via a distinct epitope to the platelet integrin α IIb β 3 receptor, therapeutic agents (including antibodies), that block CD11b binding epitope to fibrin can reduce the damaging effects of fibrin in the nervous system without affecting its beneficial effects in blood coagulation. Therefore, safe, effective antibodies that inhibit fibrin

induced microglial activation without affecting its beneficial effects in blood coagulation are needed as therapeutics for degenerative neuronal disorders that involve inflammatory demyelination.

SUMMARY

[0006] In certain aspects, described herein are isolated antibodies that binds human fibrin or fibrinogen γ C domain, comprising a heavy chain comprising a variable heavy (VH) chain sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a light chain comprising a variable light (VL) chain sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein: CDR-H1 comprises the sequence set forth in SEQ ID NO: 1, 13, 25, 37, 49, 61, 73, 85, 97, 109, 121, 133, 145, 157, 169, 181, 193, 205, 217, or 229; CDR-H2 comprises the sequence set forth in SEQ ID NO: 2, 14, 26, 38, 50, 62, 74, 86, 98, 110, 122, 134, 146, 158, 170, 182, 194, 206, 218, or 230; CDR-H3 comprises the sequence set forth in SEQ ID NO: 3, 15, 27, 39, 51, 63, 75, 87, 99, 111, 123, 135, 147, 159, 171, 183, 195, 207, 219, or 231; CDR-L1 comprises the sequence set forth in SEQ ID NO: 4, 16, 28, 40, 52, 64, 76, 88, 100, 112, 124, 136, 148, 160, 172, 184, 196, 208, 220, or 232; CDR-L2 comprises the sequence set forth in SEQ ID NO: 5, 17, 29, 41, 53, 65, 77, 89, 101, 113, 125, 137, 149, 161, 173, 185, 197, 209, 221, or 233; and CDR-L3 comprises the sequence set forth in SEQ ID NO: 6, 18, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138, 150, 162, 174, 186, 198, 210, 222, or 234.

[0007] In certain embodiments, the antibody comprises a VH sequence selected from a sequence set forth in one of SEQ ID NOs: 7, 19, 31, 43, 55, 67, 79, 91, 103, 115, 127, 139, 151, 163, 175, 187, 199, 211, 223, or 235. In certain embodiments, the antibody comprises a VL sequence selected from a sequence set forth in SEQ ID NO 10, 22, 34, 46, 58, 70, 82, 94, 106, 118, 130, 142, 154, 166, 178, 190, 202, 214, 226, or 238.

[0008] In certain embodiments, the antibody comprises a VH sequence selected from a sequence set forth in one of SEQ ID Nos: 7, and the VL sequence set for in SEQ ID NO: 10. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 19 and a VL sequence set forth in SEQ ID NO: 22. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 31 and a VL sequence set forth in SEQ ID NO: 34. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 43 and a VL sequence set forth in SEQ ID NO: 46. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 55 and a VL sequence set forth in SEQ ID NO: 58. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 67 and a VL sequence set forth in SEQ ID NO: 70. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 79 and a VL sequence set forth in SEQ ID NO: 82. In certain embodiments, the antibody comprises a VH sequence set forth

in SEQ ID NO: 91 and a VL sequence set forth in SEQ ID NO: 94. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 103 and a VL sequence set forth in SEQ ID NO: 106. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 115 and a VL sequence set forth in SEQ ID NO: 118. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 127 and a VL sequence set forth in SEQ ID NO: 130. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 139 and a VL sequence set forth in SEQ ID NO: 142. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 151 and a VL sequence set forth in SEQ ID NO: 154. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 163 and a VL sequence set forth in SEQ ID NO: 166. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 175 and a VL sequence set forth in SEQ ID NO: 178. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 187 and a VL sequence set forth in SEQ ID NO: 190. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 199 and a VL sequence set forth in SEQ ID NO: 202. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 211 and a VL sequence set forth in SEQ ID NO: 214. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 223 and a VL sequence set forth in SEQ ID NO: 226. In certain embodiments, the antibody comprises a VH sequence set forth in SEQ ID NO: 235 and a VL sequence set forth in SEQ ID NO: 238.

[0009] In certain embodiments, the antibody comprises a humanized, human or chimeric antibody. In certain embodiments, the antibody comprises a humanized antibody. In certain embodiments, the antibody comprises a heavy chain human constant region of a class selected from IgG, IgA, IgD, IgE, and IgM. In certain embodiments, the human Fc region comprises a human heavy chain constant region of the class IgG and a subclass selected from IgG1, IgG2, IgG3, and IgG4. In certain embodiments, the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the human Fc domain comprises a sequence set forth in SEQ ID NO: 8, 20, 32, 44, 56, 68, 80, 92, 104, 116, 128, 140, 152, 164, 176, 188, 200, 212, 224, or 236.

[0010] In certain embodiments, the heavy chain comprises a constant heavy chain sequence set forth by SEQ ID NO: 8, 20, 32, 44, 56, 68, 80, 92, 104, 116, 128, 140, 152, 164, 176, 188, 200, 212, 224, or 236. In certain embodiments, the light chain comprises a constant light chain sequence set forth by SEQ ID NO: 9, 21, 33, 45, 57, 69, 81, 93, 105, 117, 129, 141, 153, 165, 177, 189, 201, 213, 225, or 237.

[0011] In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 7, and the VL sequence set forth in SEQ ID NO: 10; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 19, and the VL sequence set forth in SEQ ID NO: 22; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 31, and the VL sequence set forth in SEQ ID NO: 34; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 43, and the VL sequence set forth in SEQ ID NO: 46; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 55, and the VL sequence set forth in SEQ ID NO: 58; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 67, and the VL sequence set forth in SEQ ID NO: 70; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 79, and the VL sequence set forth in SEQ ID NO: 82; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 91, and the VL sequence set forth in SEQ ID NO: 94; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 103, and the VL sequence set forth in SEQ ID NO: 106; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 115, and the VL sequence set forth in SEQ ID NO: 118; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 127, and the VL sequence set forth in SEQ ID NO: 130; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 139, and the VL sequence set forth in SEQ ID NO: 142; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 151, and the VL sequence set forth in SEQ ID NO: 154; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 163, and the VL sequence set forth in SEQ ID NO: 166; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 175, and the VL sequence set forth in SEQ ID NO: 178; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ

ID NO: 187, and the VL sequence set forth in SEQ ID NO: 190; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 199, and the VL sequence set forth in SEQ ID NO: 202; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 211, and the VL sequence set forth in SEQ ID NO: 214; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 223, and the VL sequence set forth in SEQ ID NO: 226; and the human Fc region comprises wild-type, human IgG1 Fc. In certain embodiments, the antibody comprises the VH sequence set forth in SEQ ID NO: 235, and the VL sequence set forth in SEQ ID NO: 238; and the human Fc region comprises wild-type, human IgG1 Fc.

[0012] In certain embodiments, the Fc region comprises one or more amino acid substitutions, wherein the one or more substitutions result in increased antibody half-life, increased ADCC activity, increased ADCP activity, or increased CDC activity compared with the Fc without the one or more substitutions. In certain embodiments, the Fc region binds an Fc γ Receptor selected from the group consisting of: Fc γ RI, Fc γ RIIa, Fc γ RIIb, Fc γ RIIc, Fc γ RIIIa, and Fc γ RIIIb.

[0013] In certain embodiments, the antibody is a monoclonal antibody. In certain embodiments, the antibody binds an γ 377-395 epitope of the fibrin or fibrinogen γ C domain. In certain embodiments, the antibody binds to a peptide comprising an amino acid sequence set forth in at least one of SEQ ID NOs: 241, and 249-253 with a K_D of less than or equal to about 1, 2, 3, 4, 5, 6, 7, or 8×10^{-5} M, as measured by surface plasmon resonance (SPR) single cycle kinetics (SCK) assay. In certain embodiments, the antibody binds to a peptide comprising the sequence of the γ 377-395 epitope of the human fibrin or fibrinogen γ C domain with a K_D of less than or equal to about 8×10^{-5} M, as measured by surface plasmon resonance (SPR) single cycle kinetics (SCK) assay. In certain embodiments, the antibody inhibits Mac-1 binding to fibrin or fibrinogen γ C domain. In certain embodiments, the antibody exhibits inhibition of microglial adhesion to the fibrin or fibrinogen γ C domain.

[0014] In certain aspects, described herein are the isolated antibodies of any one of the above claims for use in the treatment of a degenerative disorder of the nervous system.

[0015] In certain aspects, described herein are isolated polynucleotides or sets of polynucleotides encoding the antibody of any of the above claims, a VH thereof, a VL thereof, a light chain thereof, a heavy chain thereof, or an antigen-binding portion thereof; optionally cDNA.

[0016] In certain aspects, described herein are vectors or sets of vectors comprising the polynucleotide or set of polynucleotides described herein.

[0017] In certain aspects, described herein is a host cell comprising the polynucleotide or set of polynucleotides, or the vector or set of vectors described herein.

[0018] In certain aspects, described herein are methods of producing an antibody, the method comprising expressing the antibody with the host cell described herein and isolating the expressed antibody.

[0019] In certain aspects, described herein are pharmaceutical compositions comprising an antibody described herein and a pharmaceutically acceptable excipient.

[0020] In certain aspects, described herein are kits comprising the described herein or a pharmaceutical composition described herein and instructions for use

[0021] In certain aspects, described herein are methods for treating a degenerative disorder of the nervous system, the method comprising administering to a mammalian subject a therapeutically effective amount an antibody described herein or a pharmaceutical composition described herein. In certain embodiments, the degenerative disorder of the nervous system is selected from the group consisting of: multiple sclerosis, spinal cord injury, stroke, and Alzheimer's Disease.

[0022] In certain aspects, described herein are methods for treating a pathology associated with Mac-1 binding to fibrin or Mac-1 binding with fibrinogen, the method comprising administering to a mammalian subject a therapeutically effective amount an antibody or a pharmaceutical composition described herein.

[0023] In certain aspects, described herein are methods of inhibiting microglia activation, the method comprising administering to a mammalian subject a therapeutically effective amount an antibody or a pharmaceutical composition described herein.

[0024] In certain aspects, described herein are methods of preventing a degenerative disorder of the nervous system, the method comprising administering to a mammalian subject a therapeutically effective amount an antibody or a pharmaceutical composition described herein.

[0025] In certain aspects, described herein are methods of treating colitis in a subject in need thereof, the method comprising administering to a mammalian subject a therapeutically effective amount an antibody or a pharmaceutical composition described herein. In certain aspects, described herein are methods of preventing colitis in a subject in need thereof, the method comprising administering to a mammalian subject a therapeutically effective amount an antibody or a pharmaceutical composition described herein. In certain aspects, described herein are methods of treating a inflammatory condition of the eye in a subject in need thereof, the method comprising administering to a mammalian subject a therapeutically effective amount an antibody or a pharmaceutical composition described herein. In certain aspects, described herein are methods of preventing an inflammatory

condition of the eye in a subject in need thereof, the method comprising administering to a mammalian subject a therapeutically effective amount an antibody or a pharmaceutical composition described herein. In certain embodiments, the inflammatory condition of the eye is uveitis.

[0026] In certain aspects, described herein are isolated antibodies that bind human fibrin or fibrinogen γ C domain, wherein the antibody binds human fibrin at any one of amino acid residues Lys 411, Ile 412, Ile 413, Phe 415, Asn 416, Arg 417, Leu 418, Thr 419, Ile 420, and Gly 421. In certain embodiments, wherein the antibody binds human fibrin at at least two, three, four, five, six, seven, eight, nine, or all ten of amino acid residues Lys 411, Ile 412, Ile 413, Phe 415, Asn 416, Arg 417, Leu 418, Thr 419, Ile 420, and Gly 421.

[0027] In certain embodiments, described herein are antibodies comprising a VH region comprising a paratope that comprises any one of amino acid residues Ser 31, Tyr 32, Trp 33, His 35, Trp 47, Leu 50, Asp 52, Asp 54, Tyr 56, Ala 93, Ser 94, Ser 95, Lys 96 or Asp 96, Pro 97 or Ala 97, Gly 101, Gly102, and Trp 103. In certain embodiments, the antibody comprises a VH region comprising a paratope that comprises at least two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, or all seventeen of amino acid residues Ser 31, Tyr 32, Trp 33, His 35, Trp 47, Leu 50, Asp 52, Asp 54, Tyr 56, Ala 93, Ser 94, Ser 95, Lys 96 or Asp 96, Pro 97 or Ala 97, Gly 101, Gly102, and Trp 103. In certain embodiments, the antibody comprises a VH region comprising a paratope that comprises amino acid residues Ser 31, Trp 33, His 35, Asp 52, Asp 54, Tyr 56, Ser 94, Gly 101, Gly102, and Trp 103. In certain embodiments, the antibody comprises a VH region comprising a paratope that comprises amino acid residues Ser 31, Trp 33, His 35, Asp 52, Asp 54, Tyr 56, Ala 93, Ser 94, Lys 96, Pro 97, Gly 101, Gly102, and Trp 103. In certain embodiments, the antibody comprises a VH region comprising a paratope that comprises amino acid residues Ser 31, Tyr 32, Trp 33, His 35, Trp 47, Asp 52, Asp 54, Tyr 56, Ser 94, Ser 95, Asp 96, Ala 97, Gly 101, Gly102, and Trp 103.

[0028] In certain embodiments, described herein are isolated antibodies, wherein the antibody comprises a VL region comprising a paratope that comprises any one of amino acid residues His 27, Tyr 32, Tyr 36, Leu 46, Tyr 49, Gln 50, Ala 91 or Asn 91, Leu 92, Leu 94, and Leu 96. In certain embodiments, the antibody comprises a VL region comprising a paratope that comprises at least two, three, four, five, six, seven, eight, nine or all ten amino acid residues His 27, Tyr 32, Tyr 36, Leu 46, Tyr 49, Gln 50, Ala 91 or Asn 91, Leu 92, Leu 94, and Leu 96. In certain embodiments, the antibody comprises a VL region comprising a paratope that comprises the amino acid residues His 27, Tyr 32, Tyr 36, Leu 46, Gln 50, Leu 92, Leu 94, and Leu 96. In certain embodiments, the antibody comprises a VL region comprising a paratope that comprises the amino acid residues His 27, Tyr 32, Tyr 36,

Leu 46, Gln 50, Asn 91, Leu 92, Leu 94, and Leu 96. In certain embodiments, the antibody comprises a VL region comprising a paratope that comprises the amino acid residues His 27, Tyr 32, Tyr 36, Leu 46, Tyr 49, Gln 50, Ala 91, Leu 92, Leu 94, and Leu 96.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0029] These and other features, aspects, and advantages of the present invention will become better understood with regard to the following description, and accompanying drawings, where:

[0030] **Figure 1** are plots from FACS analysis of antibody library binding to N-terminally biotinylated fibrin P2 gamma peptide showing results of three rounds of antibody affinity maturation with one library produced from one of the three parental humanized antibodies (clone 56657).

[0031] **Figure 2A** is a graph showing the results of an enzyme-linked immunosorbant assay (ELISA) performed with the indicated humanized antibody variants and P2 peptide. A= clone 60143; B= clone 61278; C= clone 61278(duplicate); D= parental antibody.

[0032] **Figure 2B** is a graph showing the results of an enzyme-linked immunosorbant assay (ELISA) performed with the indicated humanized antibody variants and FG (fibrinogen). A= clone 60143; B= clone 61278; C= clone 61278 (duplicate); D= parental antibody.

[0033] **Figure 2C** is a graph showing the results of an enzyme-linked immunosorbant assay (ELISA) performed with the indicated humanized antibody variants and fibrin. A= clone 60143; B= clone 61278; C= clone 61278 (duplicate); D= parental antibody.

[0034] **Figure 3A and 3B** are graphs showing the results of an assay demonstrating clot lysis time of samples in the presence of variant humanized antibodies. A= clone 56666; B= clone 56657; C= clone 60143; D=clone 60181; E=clone 60175; F=clone 60163; G=clone 60173; H=clone 60184; I=clone 60141; J=clone 60179; K=clone 60140; L=clone 60183.

[0035] **Figure 4** are graphs showing the results of ForteBio K_D measurements described herein with either N-terminally biotinylated fibrin P2 gamma peptide conjugated to IgG in solution (100 nM) or FAB (monovalent) in solution (100 nM). The antibody clones tested are indicated.

[0036] **Figure 5** are graphs showing results of octet Fab binding to N-terminally biotinylated Fibrin P2 gamma peptide on SA sensor with 100 mM Fab in solution. The antibody clones tested are indicated.

[0037] **Figure 6** are graphs showing staining of brain tissue sections from a fibrinogen induced encephalomyelitis (FIE) mouse model injected I.V with artificial cerebral spinal fluid (acsf), fibrinogen alone, or fibrinogen and the indicated antibody clones at either 10 mg/Kg ("10") or 30

mg/Kg ("30"). Sections were stained with either Iba-1 (left) (microglial marker at 1:750 dilution) or Mac-2 (right) (macrophage infiltration marker at 1:750 dilution).

[0038] **Figure 7** is a graph showing clinical score of mice from an experimental autoimmune encephalomyelitis (EAE) model that were subjected to prophylactic injection of PBS alone, IgG1 alone, antibody clone 60143, antibody clone 61278, or dexamethasone. Antibodies were injected by intraperitoneal injection at 5 mg/kg every 3 days.

[0039] **Figure 8** shows graphs of onset of disease (left) and paralysis rate (right) of mice from an experimental autoimmune encephalomyelitis (EAE) model that were subjected to prophylactic injection of PBS alone, IgG1 alone, antibody clone 60143, antibody clone 61278, or dexamethasone. Antibodies were injected by intraperitoneal injection at 5 mg/kg every 3 days.

[0040] **Figure 9** are graphs showing clinical score of mice from an experimental autoimmune encephalomyelitis (EAE) model that were subjected to prophylactic injection of PBS alone, dexamethasone, antibody clone 60143 (left) or control antibody human IgG1 (right).

[0041] **Figure 10** are graphs showing proportion of paralyzed mice (complete paralysis- left) or (partial hindlimb paralysis- right) from an experimental autoimmune encephalomyelitis (EAE) model that were subjected to prophylactic injection of PBS alone, dexamethasone (dexa), antibody clone 6043 (at the indicated concentrations; 5= 5 mg/kg, 1= 1 mg/kg and 0.2=0.2 mg/kg) or control antibody human IgG1 (5 mg/kg).

[0042] **Figure 11** is a diagram showing the gene expression assay workflow for the BMDM cell line.

[0043] **Figure 12** are graphs showing interleukin (IL)-12b expression in BMDM cells after incubation with fibrinogen and fibrin, IgG1, antibody clone 60143 and antibody clone 61278 at either 50ug/mL (left) or 10ug/ml (right) antibody.

[0044] **Figure 13** are graphs showing interleukin (IL)-12b expression in BMDM cells after incubation with the indicated concentrations of fibrinogen and antibody clone 61278 (left) or antibody clone 60143 (right).

[0045] **Figure 14** is a graph showing reduced physiological symptoms of colitis in a dextran sodium sulfate (DSS)-induced mouse model of colitis in animals injected intravenously with 5 mg/kg or 30 mg/kg antibody clone 60143 or isotype control antibody human IgG1.

[0046] **Figure 15A** and **figure 15B** shows uptake (%ID) of [¹²⁵I]SIB-60143 and [¹²⁵I]SIB-61278 injected at 10 mg/kg and 30 mg/kg in mice blood (A) and plasma (B), corrected for theoretical blood and plasma volumes.

[0047] **Figure 16A, figure 16B, figure 16C, and figure 16D** show ex vivo biodistribution of [^{125} I]SIB-60143 (A and B) and [^{125} I]SIB-61278 (C and D) injected at 10 mg/kg (A and C) and 30 mg/kg (B and D) in mice over time.

[0048] **Figure 17** is a diagram depicting the crystal structure of the Fab of antibody clone 60143 (ADI60143) and antibody clone 61278 (ADI61278) in complex with P2 peptide (co-crystal- right). The structure of Fibrinogen (FGG) and the location of P2-peptide are also shown (bottom left).

[0049] **Figure 18** is a diagram depicting the superimposed structures of the Fab of antibody clone 60143 (ADI60143) and antibody clone 61278 (ADI61278) in complex with P2 peptide.

[0050] **Figure 19** is a graph depicting the binding affinity of antibody clone 60143 (ADI60143) and antibody clone 61278 (ADI61278). The binding of the ADI-60143 and ADI-61278 Fabs to P2 peptide was determined using Octet RED384.

[0051] (Figures 21 and 22), and similar binding profiles were observed for the three P2 peptides from the different species. However, the extended P2 peptide of the three species, did not bind well to ADI-60143 Fab (Figure 22).

[0052] **Figure 20A** is a graph depicting binding of ADI-60143 Fab to rat, mouse or human P2 peptide determined by ELISA.

[0053] **Figure 20B** is a graph depicting binding of ADI-60143 IgG to rat, mouse or human P2 peptide determined by ELISA.

[0054] **Figure 21** are graphs depicting Binding of ADI-60143 IgG to rat, mouse or human extended P2 peptide determined by ELISA.

[0055] **Figure 22A** is a diagram depicting the experimental protocol performed for determining microglial activation and macrophage recruitment in the Fibrin induced encephalitis (FIE) mouse model.

[0056] **Figure 22B** is a graph depicting percent area of Iba-1 positive staining for determining microglial activation in brain tissue sections from FIE mice administered acsf (artificial cerebral spinal fluid), fibrinogen, IgG isotype control (30 mg/Kg), parental humanized antibody clone THN227 (not affinity matured) (10 or 30 mg/Kg), and affinity matured antibody clone ADI-60143 (10 or 30 mg/Kg).

[0057] **Figure 22C** is a graph depicting percent area of Mac-2 positive staining for determining macrophage infiltration in brain tissue sections from FIE mice administered acsf (artificial cerebral spinal fluid), fibrinogen, IgG isotype control (30 mg/Kg), parental humanized antibody clone THN227 (not affinity matured) (10 or 30 mg/Kg), and affinity matured antibody clone ADI-60143 (10 or 30 mg/Kg).

[0058] **Figure 23** are images showing tissue sections from spinal cords of healthy and EAE mice stained for ADI-60143.

[0059] **Figure 24A** is a graph depicting demyelination determined by MBP staining of tissue sections from spinal cords of EAE mice administered PBS, dexamethasone (DEXA), and 0.2, 1 or 5 mg/Kg antibody clone ADI-60143.

[0060] **Figure 24B** is a graph depicting percent of EAE mice exhibiting complete hindlimb paralysis administered PBS, dexamethasone (DEXA), and 0.2, 1 or 5 mg/Kg antibody clone ADI-60143.

[0061] **Figure 25** is a graph depicting clinical score of EAE mice administered isotype control, antibody clone ADI-60143 IgG, and antibody clone ADI-60143-with Fc stabilization LALA mutations, and naïve mice with no EAE induction.

[0062] **Figure 26A** is a graph depicting the average number of total inflammatory foci/spinal cord tissue section of EAE mice administered isotype control, antibody clone ADI-60143 IgG, and antibody clone ADI-60143-with Fc stabilization LALA mutations, and naïve mice with no EAE induction.

[0063] **Figure 26B** is a graph depicting the percent CD11b+ area per tissue section of EAE mice administered isotype control, antibody clone ADI-60143 IgG, and antibody clone ADI-60143-with Fc stabilization LALA mutations, and naïve mice with no EAE induction.

[0064] **Figure 27** is a graph depicting the uveitis clinical score of rats administered intravitreally isotype control, murinized antibody clone ADI-60143-with Fc stabilization LALA mutations (low dose = 10 ug/eye; high dose = 50 ug/eye), positive control FTY-720 (administered by oral gavage at a dose of 0.3 mg/kg) and naïve mice with no EAE induction.

DETAILED DESCRIPTION

Definitions

[0065] Unless otherwise defined, all terms of art, notations and other scientific terminology used herein are intended to have the meanings commonly understood by those of skill in the art. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a difference over what is generally understood in the art. The techniques and procedures described or referenced herein are generally well understood and commonly employed using conventional methodologies by those skilled in the art, such as, for example, the widely utilized molecular cloning methodologies described in Sambrook et al., *Molecular Cloning: A Laboratory Manual* 4th ed. (2012) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY. As appropriate, procedures involving

the use of commercially available kits and reagents are generally carried out in accordance with manufacturer-defined protocols and conditions unless otherwise noted.

[0066] As used herein, the singular form “a”, “an”, and “the” includes plural references unless indicated otherwise.

[0067] It is understood that aspects and embodiments of the invention described herein include “comprising,” “consisting,” and “consisting essentially of” aspects and embodiments.

[0068] For all compositions described herein, and all methods using a composition described herein, the compositions can either comprise the listed components or steps, or can “consist essentially of” the listed components or steps. When a composition is described as “consisting essentially of” the listed components, the composition contains the components listed, and may contain other components which do not substantially affect the condition being treated, but do not contain any other components which substantially affect the condition being treated other than those components expressly listed; or, if the composition does contain extra components other than those listed which substantially affect the condition being treated, the composition does not contain a sufficient concentration or amount of the extra components to substantially affect the condition being treated. When a method is described as “consisting essentially of” the listed steps, the method contains the steps listed, and may contain other steps that do not substantially affect the condition being treated, but the method does not contain any other steps which substantially affect the condition being treated other than those steps expressly listed. As a non-limiting specific example, when a composition is described as “consisting essentially of” a component, the composition may additionally contain any amount of pharmaceutically acceptable carriers, vehicles, or diluents and other such components which do not substantially affect the condition being treated.

[0069] The term “vector,” as used herein, refers to a nucleic acid molecule capable of propagating another nucleic acid to which it is linked. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has been introduced. Certain vectors are capable of directing the expression of nucleic acids to which they are operatively linked. Such vectors are referred to herein as “expression vectors.”

[0070] The terms “host cell,” “host cell line,” and “host cell culture” are used interchangeably and refer to cells into which an exogenous nucleic acid has been introduced, and the progeny of such cells. Host cells include “transformants” (or “transformed cells”) and “transfectants” (or “transfected cells”), which each include the primary transformed or transfected cell and progeny derived therefrom. Such progeny may not be completely identical in nucleic acid content to a parent cell, and may contain mutations. A “recombinant host cell” or “host cell” refers to a cell that includes an

exogenous polynucleotide, regardless of the method used for insertion, for example, direct uptake, transduction, f-mating, or other methods known in the art to create recombinant host cells.

[0071] As used herein, the term “eukaryote” refers to organisms belonging to the phylogenetic domain Eucarya such as animals (including but not limited to, mammals, insects, reptiles, birds, etc.), ciliates, plants (including but not limited to, monocots, dicots, algae, etc.), fungi, yeasts, flagellates, microsporidia, protists, etc.

[0072] As used herein, the term “prokaryote” refers to prokaryotic organisms. For example, a non-eukaryotic organism can belong to the Eubacteria (including but not limited to, *Escherichia coli*, *Thermus thermophilus*, *Bacillus stearothermophilus*, *Pseudomonas fluorescens*, *Pseudomonas aeruginosa*, *Pseudomonas putida*, etc.) phylogenetic domain, or the Archaea (including but not limited to, *Methanococcus jannaschii*, *Methanobacterium thermoautotrophicum*, *Halobacterium* such as *Haloferax volcanii* and *Halobacterium* species NRC-1, *Archaeoglobus fulgidus*, *Pyrococcus furiosus*, *Pyrococcus horikoshii*, *Aeuropyrum pernix*, etc.) phylogenetic domain.

[0073] An “effective amount” or “therapeutically effective amount” as used herein refers to an amount of therapeutic compound, such as an anti-FIBRIN antibody, administered to an individual, either as a single dose or as part of a series of doses, which is effective to produce or contribute to a desired therapeutic effect, either alone or in combination with another therapeutic modality. Examples of a desired therapeutic effect is enhancing an immune response, slowing or delaying tumor development; stabilization of disease; amelioration of one or more symptoms. An effective amount may be given in one or more dosages.

[0074] The term “treating” (and variations thereof such as “treat” or “treatment”) refers to clinical intervention in an attempt to alter the natural course of a disease or condition in a subject in need thereof. Treatment can be performed during the course of clinical pathology. Desirable effects of treatment include preventing recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis.

[0075] The term “sufficient amount” means an amount sufficient to produce a desired effect, e.g., an amount sufficient to modulate an immune response in a subject.

[0076] As used herein, the term “subject” or “individual” means a mammalian subject. Exemplary subjects include humans, monkeys, dogs, cats, mice, rats, cows, horses, camels, goats, rabbits, and sheep. In certain embodiments, the subject is a human. In some embodiments the subject has a disease

or condition that can be treated with an antibody provided herein. In some aspects, the disease or condition is a cancer. In some aspects, the disease or condition is a viral infection.

[0077] The term “in vitro” refers to processes that occur in a living cell growing separate from a living organism, e.g., growing in tissue culture.

[0078] The term “in vivo” refers to processes that occur in a living organism.

[0079] The term “package insert” is used to refer to instructions customarily included in commercial packages of therapeutic or diagnostic products (e.g., kits) that contain information about the indications, usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic or diagnostic products.

[0080] The term “pharmaceutical composition” refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective in treating a subject, and which contains no additional components which are unacceptably toxic to the subject in the amounts provided in the pharmaceutical composition.

[0081] The terms “co-administration”, “co-administer”, and “in combination with” include the administration of two or more therapeutic agents either simultaneously, concurrently or sequentially within no specific time limits. In one embodiment, the agents are present in the cell or in the subject's body at the same time or exert their biological or therapeutic effect at the same time. In one embodiment, the therapeutic agents are in the same composition or unit dosage form. In other embodiments, the therapeutic agents are in separate compositions or unit dosage forms. In certain embodiments, a first agent can be administered prior to the administration of a second therapeutic agent.

[0082] The terms “modulate” and “modulation” refer to reducing or inhibiting or, alternatively, activating or increasing, a recited variable.

[0083] The terms “increase” and “activate” refer to an increase of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, or greater in a recited variable.

[0084] The terms “reduce” and “inhibit” refer to a decrease of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, or greater in a recited variable.

[0085] The term “about” indicates and encompasses an indicated value and a range above and below that value. In certain embodiments, the term “about” indicates the designated value $\pm 10\%$, $\pm 5\%$, or $\pm 1\%$. In certain embodiments, where applicable, the term “about” indicates the designated value(s) $\pm$ one standard deviation of that value(s).

[0086] The term “agonize” refers to the activation of receptor signaling to induce a biological response associated with activation of the receptor. An “agonist” is an entity that binds to and agonizes a receptor.

[0087] The term “antagonize” refers to the inhibition of receptor signaling to inhibit a biological response associated with activation of the receptor. An “antagonist” is an entity that binds to and antagonizes a receptor.

[0088] For any of the structural and functional characteristics described herein, methods of determining these characteristics are known in the art.

[0089] The term “optionally” is meant, when used sequentially, to include from one to all of the enumerated combinations and contemplates all sub-combinations.

[0090] The term “amino acid” refers to the twenty common naturally occurring amino acids. Naturally occurring amino acids include alanine (Ala; A), arginine (Arg; R), asparagine (Asn; N), aspartic acid (Asp; D), cysteine (Cys; C), glutamic acid (Glu; E), glutamine (Gln; Q), Glycine (Gly; G), histidine (His; H), isoleucine (Ile; I), leucine (Leu; L), lysine (Lys; K), methionine (Met; M), phenylalanine (Phe; F), proline (Pro; P), serine (Ser; S), threonine (Thr; T), tryptophan (Trp; W), tyrosine (Tyr; Y), and valine (Val; V).

[0091] The term “affinity” refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen or epitope). Unless indicated otherwise, as used herein, “affinity” refers to intrinsic binding affinity, which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen or epitope).

[0092] The term “ k_d ” (sec^{-1}), as used herein, refers to the dissociation rate constant of a particular antibody - antigen interaction. This value is also referred to as the k_{off} value.

[0067] The term “ k_a ” ($\text{M}^{-1} \times \text{sec}^{-1}$), as used herein, refers to the association rate constant of a particular antibody -antigen interaction. This value is also referred to as the k_{on} value.

[0068] The term “ K_D ” (M), as used herein, refers to the dissociation equilibrium constant of a particular antibody -antigen interaction. $K_D = k_d/k_a$. In some embodiments, the affinity of an antibody is described in terms of the K_D for an interaction between such antibody and its antigen. For clarity, as known in the art, a smaller K_D value indicates a higher affinity interaction, while a larger K_D value indicates a lower affinity interaction.

[0069] The term “ K_A ” (M^{-1}), as used herein, refers to the association equilibrium constant of a particular antibody-antigen interaction. $K_A = k_a/k_d$.

[0070] The term “antibody” is used herein in its broadest sense and includes certain types of immunoglobulin molecules comprising one or more antigen-binding domains that specifically bind to an antigen or epitope. An antibody specifically includes intact antibodies (e.g., intact immunoglobulins), antibody fragments, and multi-specific antibodies.

[0071] A “Fibrin antibody,” “anti-Fibrin antibody,” or “Fibrin -specific antibody” is an antibody, as provided herein, which specifically binds to the antigen Fibrin. In some embodiments, the antibody binds the extracellular domain of Fibrin. In certain embodiments, a Fibrin antibody provided herein binds to an epitope of Fibrin that is conserved between or among Fibrin proteins from different species.

[0072] The term “epitope” means a portion of an antigen that specifically binds to an antibody.

[0073] The term “hypervariable region” or “HVR”, as used herein, refers to each of the regions of an antibody variable domain which are hypervariable in sequence and/or form structurally defined loops (“hypervariable loops”).

[0074] The term “antigen-binding domain” means the portion of an antibody that is capable of specifically binding to an antigen or epitope.

[0075] The term “chimeric antibody” refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[0076] The term “human antibody” refers to an antibody which possesses an amino acid sequence corresponding to that of an antibody produced by a human or a human cell, or derived from a non-human source that utilizes a human antibody repertoire or human antibody-encoding sequences (e.g., obtained from human sources or designed de novo). Human antibodies specifically exclude humanized antibodies.

[0077] The term “humanized antibody” refers to a protein having a sequence that differs from the sequence of an antibody derived from a non-human species by one or more amino acid substitutions, deletions, and/or additions, such that the humanized antibody is less likely to induce an immune response, and/or induces a less severe immune response, as compared to the non-human species antibody, when it is administered to a human subject.

[0078] The term “multispecific antibody” refers to an antibody that comprises two or more different antigen-binding domains that collectively specifically bind two or more different epitopes.

[0079] A “monospecific antibody” is an antibody that comprises one or more binding sites that specifically bind to a single epitope. An example of a monospecific antibody is a naturally occurring IgG molecule which, while divalent (i.e., having two antigen-binding domains), recognizes the same

epitope at each of the two antigen-binding domains. The binding specificity may be present in any suitable valency.

[0080] The term “monoclonal antibody” refers to an antibody from a population of substantially homogeneous antibodies. A population of substantially homogeneous antibodies comprises antibodies that are substantially similar and that bind the same epitope(s), except for variants that may normally arise during production of the monoclonal antibody. Such variants are generally present in only minor amounts. A monoclonal antibody is typically obtained by a process that includes the selection of a single antibody from a plurality of antibodies. For example, the selection process can be the selection of a unique clone from a plurality of clones, such as a pool of hybridoma clones, phage clones, yeast clones, bacterial clones, or other recombinant DNA clones. The selected antibody can be further altered, for example, to improve affinity for the target (“affinity maturation”), to humanize the antibody, to improve its production in cell culture, and/or to reduce its immunogenicity in a subject.

[0081] The term “single-chain” refers to a molecule comprising amino acid monomers linearly linked by peptide bonds. In a particular such embodiment, the C-terminus of the Fab light chain is connected to the N-terminus of the Fab heavy chain in the single-chain Fab molecule. As described in more detail herein, an scFv has a variable domain of light chain (VL) connected from its C-terminus to the N-terminal end of a variable domain of heavy chain (VH) by a polypeptide chain. Alternately the scFv comprises of polypeptide chain where in the C-terminal end of the VH is connected to the N-terminal end of VL by a polypeptide chain.

[0082] The “Fab fragment” (also referred to as fragment antigen-binding) contains the constant domain (CL) of the light chain and the first constant domain (CH1) of the heavy chain along with the variable domains VL and VH on the light and heavy chains respectively. The variable domains comprise the complementarity determining loops (CDR, also referred to as hypervariable region) that are involved in antigen-binding. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region.

[0083] “F(ab')₂” fragments contain two Fab' fragments joined, near the hinge region, by disulfide bonds. F(ab')₂ fragments may be generated, for example, by recombinant methods or by pepsin digestion of an intact antibody. The F(ab') fragments can be dissociated, for example, by treatment with β-mercaptoethanol.

[0084] “Fv” fragments comprise a non-covalently-linked dimer of one heavy chain variable domain and one light chain variable domain.

[0085] “Single-chain Fv” or “sFv” or “scFv” includes the VH and VL domains of an antibody, wherein these domains are present in a single polypeptide chain. In one embodiment, the Fv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the scFv to form the desired structure for antigen-binding. For a review of scFv see Pluckthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994). HER2 antibody scFv fragments are described in WO93/16185; U.S. Pat. No. 5,571,894; and U.S. Pat. No. 5,587,458.

[0086] “scFv-Fc” fragments comprise an scFv attached to an Fc domain. For example, an Fc domain may be attached to the C-terminal of the scFv. The Fc domain may follow the VH or VL, depending on the orientation of the variable domains in the scFv (i.e., VH -VL or VL -VH). Any suitable Fc domain known in the art or described herein may be used. In some cases, the Fc domain comprises an IgG4 Fc domain.

[0087] The term “single domain antibody” or “sdAb” refers to a molecule in which one variable domain of an antibody specifically binds to an antigen without the presence of the other variable domain. Single domain antibodies, and fragments thereof, are described in Arabi Ghahroudi et al., *FEBS Letters*, 1998, 414:521-526 and Muyldermans et al., *Trends in Biochem. Sci.*, 2001, 26:230-245, each of which is incorporated by reference in its entirety. Single domain antibodies are also known as sdAbs or nanobodies. Sdabs are fairly stable and easy to express as fusion partner with the Fc chain of an antibody (Harmsen MM, De Haard HJ (2007). "Properties, production, and applications of camelid single-domain antibody fragments". *Appl. Microbiol Biotechnol.* 77(1): 13-22).

[0088] The terms “full length antibody,” “intact antibody,” and “whole antibody” are used herein interchangeably to refer to an antibody having a structure substantially similar to a naturally occurring antibody structure and having heavy chains that comprise an Fc region. For example, when used to refer to an IgG molecule, a “full length antibody” is an antibody that comprises two heavy chains and two light chains.

[0089] The term “antibody fragment” refers to an antibody that comprises a portion of an intact antibody, such as the antigen-binding or variable region of an intact antibody. Antibody fragments include, for example, Fv fragments, Fab fragments, F(ab')₂ fragments, Fab' fragments, scFv (sFv) fragments, and scFv-Fc fragments.

[0090] The term “Fc domain” or “Fc region” herein is used to define a C-terminal region of an immunoglobulin heavy chain that contains at least a portion of the constant region. The term includes native sequence Fc regions and variant Fc regions.

[0091] The term “substantially purified” refers to a construct described herein, or variant thereof that may be substantially or essentially free of components that normally accompany or interact with the protein as found in its naturally occurring environment, i.e. a native cell, or host cell in the case of recombinantly produced heteromultimer that in certain embodiments, is substantially free of cellular material includes preparations of protein having less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about 1% (by dry weight) of contaminating protein.

[0092] The term percent “identity,” in the context of two or more nucleic acid or polypeptide sequences, refer to two or more sequences or subsequences that have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned for maximum correspondence, as measured using one of the sequence comparison algorithms described below (e.g., using publicly available computer software such as BLAST, BLASTP, BLASTN, BLAST-2, ALIGN, MEGALIGN (DNASTAR), CLUSTALW, CLUSTAL OMEGA, or MUSCLE software or other algorithms available to persons of skill) or by visual inspection. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (ncbi.nlm.nih.gov). Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. Depending on the application, the percent “identity” can exist over a region of the sequence being compared, e.g., over a functional domain, or, alternatively, exist over the full length of the two sequences to be compared.

[0093] For sequence comparison, typically one sequence acts as a reference sequence to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

[0094] Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith & Waterman, *Adv. Appl. Math.* 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, *J. Mol. Biol.* 48:443 (1970), by the search for similarity method of Pearson & Lipman, *Proc. Nat'l. Acad. Sci. USA* 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by visual inspection (see generally Ausubel et al., *infra*).

[0095] Ranges recited herein are understood to be shorthand for all of the values within the range, inclusive of the recited endpoints. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, and 50.

[0096] It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise.

Anti-Fibrin Antibodies

Antibody Structure

[0097] The present application provides antibodies and compositions comprising an antibody which binds a fibrin protein.

[0098] The recognized immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon and mu constant region genes, as well as the myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. The “class” of an antibody or immunoglobulin refers to the type of constant domain or constant region possessed by its heavy chain. There are five major classes of antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α , δ , ϵ , γ , and μ , respectively.

[0099] An exemplary immunoglobulin (antibody) structural unit is composed of two pairs of polypeptide chains, each pair having one “light” (about 25 kD) and one “heavy” chain (about 50-70 kD). The N-terminal domain of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms variable light chain (VL) and variable heavy chain (VH) refer to these light and heavy chain domains respectively. The IgG1 heavy chain comprises of the VH, CH1, CH2 and CH3 domains respectively from the N to C-terminus. The light chain comprises of the VL and CL domains from N to C terminus. The IgG1 heavy chain comprises a hinge between the CH1 and CH2 domains. In certain embodiments, the immunoglobulin constructs comprise at least one immunoglobulin domain from IgG, IgM, IgA, IgD, or IgE connected to a therapeutic polypeptide. In some embodiments, the immunoglobulin domain found in an antibody provided herein, is from or derived from an immunoglobulin based construct such as a diabody, or a nanobody. In certain embodiments, the immunoglobulin constructs described herein comprise at least one immunoglobulin domain from a heavy chain antibody such as a camelid antibody. In certain embodiments, the immunoglobulin constructs provided herein comprise at least one immunoglobulin

domain from a mammalian antibody such as a bovine antibody, a human antibody, a camelid antibody, a mouse antibody or any chimeric antibody.

[00100] In some embodiments, the antibodies provided herein comprise a heavy chain. In one embodiment, the heavy chain is an IgA. In one embodiment, the heavy chain is an IgD. In one embodiment, the heavy chain is an IgE. In one embodiment, the heavy chain is an IgG. In one embodiment, the heavy chain is an IgM. In one embodiment, the heavy chain is an IgG1. In one embodiment, the heavy chain is an IgG2. In one embodiment, the heavy chain is an IgG3. In one embodiment, the heavy chain is an IgG4. In one embodiment, the heavy chain is an IgA1. In one embodiment, the heavy chain is an IgA2.

[00101] In some embodiments, an antibody is an IgG1 antibody. In some embodiments, an antibody is an IgG3 antibody. In some embodiments, an antibody is an IgG2 antibody. In some embodiments, an antibody is an IgG4 antibody.

[00102] Generally, native four-chain antibodies comprise six HVRs; three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). HVRs generally comprise amino acid residues from the hypervariable loops and/or from the complementarity determining regions (CDRs), the latter being of highest sequence variability and/or involved in antigen recognition. With the exception of CDR1 in VH, CDRs generally comprise the amino acid residues that form the hypervariable loops. Hypervariable regions (HVRs) are also referred to as “complementarity determining regions” (CDRs), and these terms are used herein interchangeably in reference to portions of the variable region that form the antigen-binding regions. This particular region has been described by Kabat et al., U.S. Dept. of Health and Human Services, Sequences of Proteins of Immunological Interest (1983) and by Chothia et al., *J Mol Biol* 196:901-917 (1987), where the definitions include overlapping or subsets of amino acid residues when compared against each other. Nevertheless, application of either definition to refer to a CDR of an antibody or variants thereof is intended to be within the scope of the term as defined and used herein. The exact residue numbers which encompass a particular CDR will vary depending on the sequence and size of the CDR. Those skilled in the art can routinely determine which residues comprise a particular CDR given the variable region amino acid sequence of the antibody.

[00103] The amino acid sequence boundaries of a CDR can be determined by one of skill in the art using any of a number of known numbering schemes, including those described by Kabat et al., *supra* (“Kabat” numbering scheme); Al-Lazikani et al., 1997, *J. Mol. Biol.*, 273:927-948 (“Chothia” numbering scheme); MacCallum et al., 1996, *J. Mol. Biol.* 262:732-745 (“Contact” numbering scheme); Lefranc et al., *Dev. Comp. Immunol.*, 2003, 27:55-77 (“IMGT” numbering

scheme); and Honegge and Plückthun, *J. Mol. Biol.*, 2001, 309:657-70 (“AHo” numbering scheme); each of which is incorporated by reference in its entirety.

[00104] **Table A** provides the positions of CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and CDR-H3 as identified by the Kabat and Chothia schemes. For CDR-H1, residue numbering is provided using both the Kabat and Chothia numbering schemes.

[00105] CDRs may be assigned, for example, using antibody numbering software, such as Abnum, available at www.bioinf.org.uk/abs/abnum/, and described in Abhinandan and Martin, *Immunology*, 2008, 45:3832-3839, incorporated by reference in its entirety.

Table A. Residues in CDRs according to Kabat and Chothia numbering schemes.

Table A		
CDR	Kabat	Chothia
L1	L24-L34	L24-L34
L2	L50-L56	L50-L56
L3	L89-L97	L89-L97
H1 (Kabat Numbering)	H31-H35B	H26-H32 or H34*
H1 (Chothia Numbering)	H31-H35	H26-H32
H2	H50-H65	H52-H56
H3	H95-H102	H95-H102

* The C-terminus of CDR-H1, when numbered using the Kabat numbering convention, varies between H32 and H34, depending on the length of the CDR.

[00106] The “EU numbering scheme” is generally used when referring to a residue in an antibody heavy chain constant region (e.g., as reported in Kabat et al., *supra*). Unless stated otherwise, the EU numbering scheme is used to refer to residues in antibody heavy chain constant regions described herein.

[00107] One example of an antigen-binding domain is an antigen-binding domain formed by a VH-VL dimer of an antibody. Another example of an antigen-binding domain is an antigen-binding domain formed by diversification of certain loops from the tenth fibronectin type III domain of an Adnectin. An antigen-binding domain can include CDRs 1, 2, and 3 from a heavy chain in that order; and CDRs 1, 2, and 3 from a light chain in that order.

[00108] Epitopes frequently consist of surface-accessible amino acid residues and/or sugar side chains and may have specific three-dimensional structural characteristics, as well as specific charge characteristics. Conformational and non-conformational epitopes are distinguished in that the binding to the former but not the latter may be lost in the presence of denaturing solvents. An epitope may comprise amino acid residues that are directly involved in the binding, and other amino acid residues, which are not directly involved in the binding. The epitope to which an antibody binds can be

determined using known techniques for epitope determination such as, for example, testing for antibody binding to Fibrin variants with different point-mutations, or to chimeric Fibrin variants.

[00109] To screen for antibodies which bind to an epitope on a target antigen bound by an antibody of interest (e.g., Fibrin), a routine cross-blocking assay such as that described in *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. Alternatively, or additionally, epitope mapping can be performed by methods known in the art.

[00110] Chimeric antibodies are antibodies in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[00111] Human antibodies are antibodies which possesses an amino acid sequence corresponding to that of an antibody produced by a human or a human cell, or derived from a non-human source that utilizes a human antibody repertoire or human antibody-encoding sequences (e.g., obtained from human sources or designed de novo). Human antibodies specifically exclude humanized antibodies.

[00112] A humanized antibody has a sequence that differs from the sequence of an antibody derived from a non-human species by one or more amino acid substitutions, deletions, and/or additions, such that the humanized antibody is less likely to induce an immune response, and/or induces a less severe immune response, as compared to the non-human species antibody, when it is administered to a human subject. In one embodiment, certain amino acids in the framework and constant domains of the heavy and/or light chains of the non-human species antibody are mutated to produce the humanized antibody. In another embodiment, the constant domain(s) from a human antibody are fused to the variable domain(s) of a non-human species. In another embodiment, one or more amino acid residues in one or more CDR sequences of a non-human antibody are changed to reduce the likely immunogenicity of the non-human antibody when it is administered to a human subject, wherein the changed amino acid residues either are not critical for immunospecific binding of the antibody to its antigen, or the changes to the amino acid sequence that are made are conservative changes, such that the binding of the humanized antibody to the antigen is not significantly worse than the binding of the non-human antibody to the antigen. Examples of how to make humanized antibodies can be found in U.S. Pat. Nos. 6,054,297, 5,886,152 and 5,877,293. For further details, see Jones et al., *Nature*, 1986, 321:522-525; Riechmann et al., *Nature*, 1988, 332:323-329; and Presta, *Curr. Op. Struct. Biol.*, 1992, 2:593-596, each of which is incorporated by reference in its entirety.

[00113] The two or more different epitopes may be epitopes on the same antigen (e.g., a single Fibrin molecule expressed by a cell) or on different antigens (e.g., different Fibrin molecules expressed by the same cell, or a Fibrin molecule and a non- Fibrin molecule). In some aspects, a multi-specific antibody binds two different epitopes (i.e., a “bispecific antibody”). In some aspects, a multi-specific antibody binds three different epitopes (i.e., a “trispecific antibody”).

[00114] Anti-Fibrin antibodies can include those described herein such as the clones set forth in the drawings and/or tables. In some embodiments, the antibody comprises an alternative scaffold. In some embodiments, the antibody consists of an alternative scaffold. In some embodiments, the antibody consists essentially of an alternative scaffold. In some embodiments, the antibody comprises an antibody fragment. In some embodiments, the antibody consists of an antibody fragment. In some embodiments, the antibody consists essentially of an antibody fragment.

[00115] In some embodiments the antibodies are monoclonal antibodies.

[00116] In some embodiments the antibodies are polyclonal antibodies.

[00117] In some embodiments the antibodies are produced by hybridomas. In other embodiments, the antibodies are produced by recombinant cells engineered to express the desired variable and constant domains.

[00118] In some embodiments the antibodies may be single chain antibodies or other antibody derivatives retaining the antigen specificity and the lower hinge region or a variant thereof.

[00119] In some embodiments the antibodies may be polyfunctional antibodies, recombinant antibodies, human antibodies, humanized antibodies, fragments or variants thereof. In particular embodiments, the antibody fragment or a derivative thereof is selected from a Fab fragment, a Fab’2 fragment, a CDR and ScFv.

[00120] In some embodiments, the antibodies are capable of forming an immune complex. For example, an immune complex can be a tumor cell covered by antibodies.

[00119] For sequence comparison, typically one sequence acts as a reference sequence to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

[00120] Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith & Waterman, Adv. Appl. Math. 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, J. Mol. Biol. 48:443 (1970), by the search for

similarity method of Pearson & Lipman, Proc. Nat'l. Acad. Sci. USA 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by visual inspection (see generally Ausubel et al., *infra*).

[00121] One example of an algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul et al., J. Mol. Biol. 215:403-410 (1990). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (www.ncbi.nlm.nih.gov/).

Sequences of Fibrin Antibodies

V_H Domains

[00122] In some embodiments, an antibody provided herein comprises a V_H sequence selected from SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 7. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 8. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 9. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 10. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 11. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 12. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 13. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 14. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 15. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 16. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 17. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 18. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 19. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 20.

[0226] In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_H sequence provided in SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20. In some embodiments, an antibody provided herein comprises a V_H sequence provided in SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20, with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this

paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

V_L Domains

[0227] In some embodiments, an antibody provided herein comprises a V_L sequence selected from SEQ ID NO: 21.

[0228] In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_L sequence provided in SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_L sequence provided in SEQ ID NO: 21 with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

V_H-V_L Combinations

[0229] In some embodiments, an antibody provided herein comprises a V_H sequence selected from SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20; and a V_L sequence selected from SEQ ID NO: 21.

[0230] In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 7 and a V_L sequence of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 8 and a V_L sequence of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 9 and a V_L sequence of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 10 and a V_L sequence of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 11 and a V_L sequence of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 12 and a V_L sequence of SEQ ID NO: 21. In some embodiments, an antibody provided herein

comprises a V_H sequence of SEQ ID NO: 13 and a V_L sequence of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 14 and a V_L sequence of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 15 and a V_L sequence of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 16 and a V_L sequence of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 17 and a V_L sequence of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 18 and a V_L sequence of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 19 and a V_L sequence of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 20 and a V_L sequence of SEQ ID NO: 21.

[0231] In certain aspects, any of SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20 can be combined with any of SEQ ID NO: 21.

[0232] In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_H sequence provided in SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20; and a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_L sequence provided in SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_H sequence provided in SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20, with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions, and a V_L sequence provided in SEQ ID NO: 21, with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

CDRs

[0233] In some embodiments, an antibody provided herein comprises one to three CDRs of a V_H domain selected from SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20. In some embodiments, an antibody provided herein comprises two to three CDRs of a V_H domain selected from SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20. In some embodiments, an

antibody provided herein comprises three CDRs of a VH domain selected from SEQ ID NOs: 37, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20. In some aspects, the CDRs are Exemplary CDRs. In some aspects, the CDRs are Kabat CDRs. In some aspects, the CDRs are Chothia CDRs. In some aspects, the CDRs are AbM CDRs. In some aspects, the CDRs are Contact CDRs. In some aspects, the CDRs are IMGT CDRs.

[0234] In some embodiments, the CDRs are CDRs having at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1, CDR-H2, or CDR-H3 of SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20. In some embodiments, the CDR-H1 is a CDR-H1 of a VH domain selected from SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some embodiments, the CDR-H2 is a CDR-H2 of a VH domain selected from SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some embodiments, the CDR-H3 is a CDR-H3 of a VH domain selected from SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated de novo according to the methods provided herein for obtaining antibodies.

[0235] In some embodiments, an antibody provided herein comprises one to three CDRs of a VL domain of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises two to three CDRs of a VL domain of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises three CDRs of a VL domain of SEQ ID NO: 21. In some aspects, the CDRs are Exemplary CDRs. In some aspects, the CDRs are Kabat CDRs. In some aspects, the CDRs are Chothia CDRs. In some aspects, the CDRs are AbM CDRs. In some aspects, the CDRs are Contact CDRs. In some aspects, the CDRs are IMGT CDRs.

[0236] In some embodiments, the CDRs are CDRs having at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1, CDR-L2, or CDR-L3 of SEQ ID NO: 21. In some embodiments, the CDR-L1 is a CDR-L1 of a VL domain of SEQ ID NO: 21, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some embodiments, the CDR-L2 is a CDR-L2 of a VL domain of SEQ ID NO: 21, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some embodiments, the CDR-L3 is a CDR-L3 of a VL domain of SEQ ID NO: 21, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid

substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0237] In some embodiments, an antibody provided herein comprises one to three CDRs of a VH domain selected from SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20 and one to three CDRs of a VL domain of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises two to three CDRs of a VH domain selected from SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20 and two to three CDRs of a VL domain of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises three CDRs of a VH domain selected from SEQ ID NOs: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20 and three CDRs of a VL domain of SEQ ID NO: 21. In some aspects, the CDRs are Exemplary CDRs. In some aspects, the CDRs are Kabat CDRs. In some aspects, the CDRs are Chothia CDRs. In some aspects, the CDRs are AbM CDRs. In some aspects, the CDRs are Contact CDRs. In some aspects, the CDRs are IMGT CDRs.

[0238] In some embodiments, an antibody provided herein comprises a CDR-H3 selected of SEQ ID NOs: 24, 25, 26, 27, 28, 29 and 30. In some aspects, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NOs: 24, 25, 26, 27, 28, 29 and 30. In some embodiments, the CDR-H3 is a CDR-H3 selected of SEQ ID NO: 24, 25, 26, 27, 28, 29 and 30, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0239] In some embodiments, an antibody provided herein comprises a CDR-H3 selected of SEQ ID NO: 24. In some aspects, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 24. In some embodiments, the CDR-H3 is a CDR-H3 selected of SEQ ID NO: 24, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the

antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0240] In some embodiments, an antibody provided herein comprises a CDR-H3 selected of SEQ ID NO: 25. In some aspects, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 25. In some embodiments, the CDR-H3 is a CDR-H3 selected of SEQ ID NO: 25, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0241] In some embodiments, an antibody provided herein comprises a CDR-H3 selected of SEQ ID NO: 26. In some aspects, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 26. In some embodiments, the CDR-H3 is a CDR-H3 selected of SEQ ID NO: 26, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0242] In some embodiments, an antibody provided herein comprises a CDR-H3 selected of SEQ ID NO: 27. In some aspects, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 27. In some embodiments, the CDR-H3 is a CDR-H3 selected of SEQ ID NO: 27, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein.

In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0243] In some embodiments, an antibody provided herein comprises a CDR-H3 selected of SEQ ID NO: 28. In some aspects, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 28. In some embodiments, the CDR-H3 is a CDR-H3 selected of SEQ ID NO: 28, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0244] In some embodiments, an antibody provided herein comprises a CDR-H3 selected of SEQ ID NO: 29. In some aspects, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 29. In some embodiments, the CDR-H3 is a CDR-H3 selected of SEQ ID NO: 29, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0245] In some embodiments, an antibody provided herein comprises a CDR-H3 selected of SEQ ID NO: 30. In some aspects, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 30. In some embodiments, the CDR-H3 is a CDR-H3 selected of SEQ ID NO: 30, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0246] In some embodiments, an antibody provided herein comprises a CDR-H3 selected of SEQ ID NO: 3. In some aspects, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 3. In some embodiments, the CDR-H3 is a CDR-H3 selected of SEQ ID NO: 3, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0247] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO: 1. In some aspects, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 1. In some embodiments, the CDR-H1 is a CDR-H1 of SEQ ID NO: 1, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0248] In some embodiments, an antibody provided herein comprises a CDR-H2 selected of SEQ ID NO: 2. In some aspects, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 2. In some embodiments, the CDR-H2 is a CDR-H2 selected of SEQ ID NO: 2, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0249] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 24 and a CDR-H2 of SEQ ID NO: 2. In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 25, a CDR-H2 of SEQ ID NO: 2, and a CDR-H1 of SEQ ID NO: 1. In some

embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 24, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 2, and the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 1. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 24, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 2, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; and the CDR-H1 is a CDR-H1 of SEQ ID NO: 1, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0250] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 25 and a CDR-H2 of SEQ ID NO: 2. In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 25, a CDR-H2 of SEQ ID NO: 2, and a CDR-H1 of SEQ ID NO: 1. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 25, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 2, and the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 1. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 25, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 2, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; and the CDR-H1 is a CDR-H1 of SEQ ID NO: 1, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0251] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 26 and a CDR-H2 of SEQ ID NO: 2. In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 26, a CDR-H2 of SEQ ID NO: 2, and a CDR-H1 of SEQ ID NO: 1. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a

CDR-H3 of SEQ ID NO: 26, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 2, and the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 1. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 26, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 2, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; and the CDR-H1 is a CDR-H1 of SEQ ID NO: 1, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0252] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 27 and a CDR-H2 of SEQ ID NO: 2. In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 27, a CDR-H2 of SEQ ID NO: 2, and a CDR-H1 of SEQ ID NO: 1. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 27, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 2, and the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 1. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 27, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 2, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; and the CDR-H1 is a CDR-H1 of SEQ ID NO: 1, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibody described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0253] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 28 and a CDR-H2 of SEQ ID NO: 2. In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 28, a CDR-H2 of SEQ ID NO: 2, and a CDR-H1 of SEQ ID NO: 1. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 28, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95%

identity with a CDR-H2 of SEQ ID NO: 2, and the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 1. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 28, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 2, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; and the CDR-H1 is a CDR-H1 of SEQ ID NO: 1, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibody described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0254] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 29 and a CDR-H2 of SEQ ID NO: 2. In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 29, a CDR-H2 of SEQ ID NO: 2, and a CDR-H1 of SEQ ID NO: 1. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 29, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 2, and the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 1. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 29, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 2, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; and the CDR-H1 is a CDR-H1 of SEQ ID NO: 1, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibody described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0255] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 30 and a CDR-H2 of SEQ ID NO: 2. In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 30, a CDR-H2 of SEQ ID NO: 2, and a CDR-H1 of SEQ ID NO: 1. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 30, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 2, and the CDR-H1 has at least about 50%, 75%, 80%, 85%,

90%, or 95% identity with a CDR-H1 of SEQ ID NO: 1. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 30, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 2, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; and the CDR-H1 is a CDR-H1 of SEQ ID NO: 1, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibody described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0256] In some embodiments, an antibody provided herein comprises a CDR-L3 of SEQ ID NO: 6. In some aspects, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NO: 6. In some embodiments, the CDR-L3 is a CDR-L3 of SEQ ID NO: 6, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0257] In some embodiments, an antibody provided herein comprises a CDR-L2 of SEQ ID NO: 5. In some aspects, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 5. In some embodiments, the CDR-L2 is a CDR-L2 of SEQ ID NO: 5, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0258] In some embodiments, an antibody provided herein comprises a CDR-L1 of SEQ ID NO: 4. In some aspects, the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-L1 is a CDR-L1 of SEQ ID NO: 4, with

up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0259] In some embodiments, an antibody provided herein comprises a CDR-L3 of SEQ ID NO: 6 and a CDR-L2 of SEQ ID NO: 5. In some embodiments, an antibody provided herein comprises a CDR-L3 of SEQ ID NO: 6, a CDR-L2 of SEQ ID NO: 5, and a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NO: 6, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 5, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-L3 is a CDR-L3 of SEQ ID NO: 6, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 of SEQ ID NO: 5, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 of SEQ ID NO: 4, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described herein are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0260] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 24, a CDR-H2 of SEQ ID NO: 2, a CDR-H1 of SEQ ID NO: 1, a CDR-L3 of SEQ ID NO: 6, a CDR-L2 of SEQ ID NO: 5, and a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 24, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 2, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 1, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NO: 6, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 5, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ

ID NO: 24, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 2, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H1 is a CDR-H1 of SEQ ID NO: 1, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L3 is a CDR-L3 of SEQ ID NO: 6, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 of SEQ ID NO: 5, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 of SEQ ID NO: 4, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0261] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 25, a CDR-H2 of SEQ ID NO: 2, a CDR-H1 of SEQ ID NO: 1, a CDR-L3 of SEQ ID NO: 6, a CDR-L2 of SEQ ID NO: 5, and a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 25, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 2, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 1, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NO: 6, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 5, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 25, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 2, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H1 is a CDR-H1 of SEQ ID NO: 1, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L3 is a CDR-L3 of SEQ ID NO: 6, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 of SEQ ID NO: 5, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 of SEQ ID NO: 4, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some

embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0262] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 26, a CDR-H2 of SEQ ID NO: 2, a CDR-H1 of SEQ ID NO: 1, a CDR-L3 of SEQ ID NO: 6, a CDR-L2 of SEQ ID NO: 5, and a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 26, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 2, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 1, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NO: 6, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 5, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 26, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 2, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H1 is a CDR-H1 of SEQ ID NO: 1, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L3 is a CDR-L3 of SEQ ID NO: 6, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 of SEQ ID NO: 5, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 of SEQ ID NO: 4, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0263] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 27, a CDR-H2 of SEQ ID NO: 2, a CDR-H1 of SEQ ID NO: 1, a CDR-L3 of SEQ ID NO: 6, a CDR-L2 of SEQ ID NO: 5, and a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 27, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 2, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 1, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NO: 6, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 5, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95%

identity with a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 27, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 2, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H1 is a CDR-H1 of SEQ ID NO: 1, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L3 is a CDR-L3 of SEQ ID NO: 6, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 of SEQ ID NO: 5, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 of SEQ ID NO: 4, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0264] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 28, a CDR-H2 of SEQ ID NO: 2, a CDR-H1 of SEQ ID NO: 1, a CDR-L3 of SEQ ID NO: 6, a CDR-L2 of SEQ ID NO: 5, and a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 28, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 2, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 1, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NO: 6, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 5, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 28, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 2, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H1 is a CDR-H1 of SEQ ID NO: 1, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L3 is a CDR-L3 of SEQ ID NO: 6, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 of SEQ ID NO: 5, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 of SEQ ID NO: 4, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some

embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0265] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 29, a CDR-H2 of SEQ ID NO: 2, a CDR-H1 of SEQ ID NO: 1, a CDR-L3 of SEQ ID NO: 6, a CDR-L2 of SEQ ID NO: 5, and a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 29, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 2, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 1, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NO: 6, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 5, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 29, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 2, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H1 is a CDR-H1 of SEQ ID NO: 1, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L3 is a CDR-L3 of SEQ ID NO: 6, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 of SEQ ID NO: 5, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 of SEQ ID NO: 4, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0266] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 30, a CDR-H2 of SEQ ID NO: 2, a CDR-H1 of SEQ ID NO: 1, a CDR-L3 of SEQ ID NO: 6, a CDR-L2 of SEQ ID NO: 5, and a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 30, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 2, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 1, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NO: 6, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 5, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95%

identity with a CDR-L1 of SEQ ID NO: 4. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 30, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 2, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H1 is a CDR-H1 of SEQ ID NO: 1, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L3 is a CDR-L3 of SEQ ID NO: 6, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 of SEQ ID NO: 5, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 of SEQ ID NO: 4, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as “variants.” In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0267] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO: 1, a CDR-H2 of SEQ ID NO: 2, a CDR-H3 of SEQ ID NO: 24, a CDR-L1 of SEQ ID NO: 4, a CDR-L2 of SEQ ID NO: 5, and a CDR-L3 of SEQ ID NO: 6.

[0268] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO: 1, a CDR-H2 of SEQ ID NO: 2, a CDR-H3 of SEQ ID NO: 25, a CDR-L1 of SEQ ID NO: 4, a CDR-L2 of SEQ ID NO: 5, and a CDR-L3 of SEQ ID NO: 6.

[0269] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO: 1, a CDR-H2 of SEQ ID NO: 2, a CDR-H3 of SEQ ID NO: 26, a CDR-L1 of SEQ ID NO: 4, a CDR-L2 of SEQ ID NO: 5, and a CDR-L3 of SEQ ID NO: 6.

[0270] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO: 1, a CDR-H2 of SEQ ID NO: 2, a CDR-H3 of SEQ ID NO: 27, a CDR-L1 of SEQ ID NO: 4, a CDR-L2 of SEQ ID NO: 5, and a CDR-L3 of SEQ ID NO: 6.

[0271] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO: 1, a CDR-H2 of SEQ ID NO: 2, a CDR-H3 of SEQ ID NO: 28, a CDR-L1 of SEQ ID NO: 4, a CDR-L2 of SEQ ID NO: 5, and a CDR-L3 of SEQ ID NO: 6.

[0272] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO: 1, a CDR-H2 of SEQ ID NO: 2, a CDR-H3 of SEQ ID NO: 29, a CDR-L1 of SEQ ID NO: 4, a CDR-L2 of SEQ ID NO: 5, and a CDR-L3 of SEQ ID NO: 6.

[0273] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO: 1, a CDR-H2 of SEQ ID NO: 2, a CDR-H3 of SEQ ID NO: 30, a CDR-L1 of SEQ ID NO: 4, a CDR-L2 of SEQ ID NO: 5, and a CDR-L3 of SEQ ID NO: 6.

Epitopes

[0274] In certain embodiments, described herein are isolated antibodies that binds human fibrin or fibrinogen γ C domain, wherein the antibody binds human fibrin at any one of amino acid residues Lys 411, Ile 412, Ile 413, Phe 415, Asn 416, Arg 417, Leu 418, Thr 419, Ile 420, and Gly 421. In certain embodiments, the antibody binds human fibrin at at least two, three, four, five, six, seven, eight, nine, or all ten of amino acid residues Lys 411, Ile 412, Ile 413, Phe 415, Asn 416, Arg 417, Leu 418, Thr 419, Ile 420, and Gly 421. In certain embodiments, the isolated antibody binds human fibrin at amino acid residues Lys 411, Ile 412, Ile 413, Phe 415, Asn 416, Arg 417, Leu 418, Thr 419, Ile 420, and Gly 421. In certain embodiments the amino acid residue of the human fibrin or fibrinogen γ C domain epitope bind the paratope of the antibody with a distance of less than 5 Angstroms or less, 4 Angstroms or less, 3 Angstroms or less, or 2 Angstroms or less.

Paratopes

[0275] In certain embodiments, the antibodies described herein comprise a VH region comprising a paratope that binds human fibrin or fibrinogen γ C domain, wherein the paratope comprises any one of amino acid residues Ser 31, Tyr 32, Trp 33, His 35, Trp 47, Leu 50, Asp 52, Asp 54, Tyr 56, Ala 93, Ser 94, Ser 95, Lys 96 or Asp 96, Pro 97 or Ala 97, Gly 101, Gly102, and Trp 103. In certain embodiments, the antibody comprises a VH region comprising a paratope that comprises at least two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, or all seventeen of amino acid residues Ser 31, Tyr 32, Trp 33, His 35, Trp 47, Leu 50, Asp 52, Asp 54, Tyr 56, Ala 93, Ser 94, Ser 95, Lys 96 or Asp 96, Pro 97 or Ala 97, Gly 101, Gly102, and Trp 103. In certain embodiments, the antibody comprises a VH region comprising a paratope that comprises amino acid residues Ser 31, Trp 33, His 35, Asp 52, Asp 54, Tyr 56, Ser 94, Gly 101, Gly102, and Trp 103. In certain embodiments, the antibody comprises a VH region comprising a paratope that comprises amino acid residues Ser 31, Trp 33, His 35, Asp 52, Asp 54, Tyr 56, Ala 93, Ser 94, Lys 96, Pro 97, Gly 101, Gly102, and Trp 103. In certain embodiments, the antibody comprises a VH region comprising a paratope that comprises amino acid residues Ser 31, Tyr 32, Trp 33, His 35, Trp 47, Asp 52, Asp 54, Tyr 56, Ser 94, Ser 95, Asp 96, Ala 97, Gly 101, Gly102, and Trp 103.

[0276] In certain embodiments, the antibody comprises a VL region comprising a paratope that comprises any one of amino acid residues His 27, Tyr 32, Tyr 36, Leu 46, Tyr 49, Gln 50, Ala 91 or

Asn 91, Leu 92, Leu 94, and Leu 96. In certain embodiments, the antibody comprises a VL region comprising a paratope that comprises at least two, three, four, five, six, seven, eight, nine or all ten amino acid residues His 27, Tyr 32, Tyr 36, Leu 46, Tyr 49, Gln 50, Ala 91 or Asn 91, Leu 92, Leu 94, and Leu 96. In certain embodiments, the antibody comprises a VL region comprising a paratope that comprises the amino acid residues His 27, Tyr 32, Tyr 36, Leu 46, Gln 50, Leu 92, Leu 94, and Leu 96. In certain embodiments, the antibody comprises a VL region comprising a paratope that comprises the amino acid residues His 27, Tyr 32, Tyr 36, Leu 46, Gln 50, Asn 91, Leu 92, Leu 94, and Leu 96. In certain embodiments, the antibody comprises a VL region comprising a paratope that comprises the amino acid residues His 27, Tyr 32, Tyr 36, Leu 46, Tyr 49, Gln 50, Ala 91, Leu 92, Leu 94, and Leu 96.

[0277] In certain embodiments the paratope of the antibody binds the amino acid residues of the human fibrin or fibrinogen γ C domain epitope with a distance of less than 5 Angstroms or less, 4 Angstroms or less, 3 Angstroms or less, or 2 Angstroms or less.

Fc Region

[0278] The structures of the Fc regions of various immunoglobulins, and the glycosylation sites contained therein, are known in the art. See Schroeder and Cavacini, J. Allergy Clin. Immunol., 2010, 125:S41-52, incorporated by reference in its entirety. The Fc region may be a naturally occurring Fc region, or an Fc region modified as described in the art or elsewhere in this disclosure.

[0279] Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat et al, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991. An "Fc polypeptide" of a dimeric Fc as used herein refers to one of the two polypeptides forming the dimeric Fc domain, i.e. a polypeptide comprising C-terminal constant regions of an immunoglobulin heavy chain, capable of stable self-association. For example, an Fc polypeptide of a dimeric IgG Fc comprises an IgG CH2 and an IgG CH3 constant domain sequence. An Fc can be of the class IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.

[0280] The terms "Fc receptor" and "FcR" are used to describe a receptor that binds to the Fc region of an antibody. For example, an FcR can be a native sequence human FcR. Generally, an FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the Fc γ RI, Fc γ RII, and Fc γ RIII subclasses, including allelic variants and alternatively spliced forms of these receptors. Fc γ RII receptors include Fc γ RIIA (an "activating receptor") and Fc γ RIIB (an "inhibiting receptor"),

which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Immunoglobulins of other isotypes can also be bound by certain FcRs (see, e.g., Janeway et al., *Immuno Biology: the immune system in health and disease*, (Elsevier Science Ltd., NY) (4th ed., 1999)). Activating receptor Fc γ RIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor Fc γ RIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain (reviewed in Daëron, *Annu. Rev. Immunol.* 15:203-234 (1997)). FcRs are reviewed in Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-92 (1991); Capel et al., *Immunomethods* 4:25-34 (1994); and de Haas et al., *J. Lab. Clin. Med.* 126:330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term “FcR” herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., *J. Immunol.* 117:587 (1976); and Kim et al., *J. Immunol.* 24:249 (1994)).

[0281] Modifications in the CH2 domain can affect the binding of FcRs to the Fc. A number of amino acid modifications in the Fc region are known in the art for selectively altering the affinity of the Fc for different Fc γ receptors. In some aspects, the Fc comprises one or more modifications to promote selective binding of Fc- γ receptors.

[0282] Exemplary mutations that alter the binding of FcRs to the Fc are listed below:

[0283] S298A/E333A/K334A, S298A/E333A/K334A/K326A (Lu Y, Vernes JM, Chiang N, et al. *J Immunol Methods.* 2011 Feb 28;365(1-2):132-41);

[0284] F243L/R292P/Y300L/V305I/P396L, F243L/R292P/Y300L/L235V/P396L (Stavenhagen JB, Gorlatov S, Tuailon N, et al. *Cancer Res.* 2007 Sep 15;67(18):8882-90; Nordstrom JL, Gorlatov S, Zhang W, et al. *Breast Cancer Res.* 2011 Nov 30;13(6):R123);

[0285] F243L (Stewart R, Thom G, Levens M, et al. *Protein Eng Des Sel.* 2011 Sep;24(9):671-8.), S298A/E333A/K334A (Shields RL, Namenuk AK, Hong K, et al. *J Biol Chem.* 2001 Mar 2;276(9):6591-604);

[0286] S239D/I332E/A330L, S239D/I332E (Lazar GA, Dang W, Karki S, et al. *Proc Natl Acad Sci U S A.* 2006 Mar 14;103(11):4005-10);

[0287] S239D/S267E, S267E/L328F (Chu SY, Vostiar I, Karki S, et al. *Mol Immunol.* 2008 Sep;45(15):3926-33);

[0288] S239D/D265S/S298A/I332E, S239E/S298A/K326A/A327H, G237F/S298A/A330L/I332E, S239D/I332E/S298A, S239D/K326E/A330L/I332E/S298A, G236A/S239D/D270L/I332E, S239E/S267E/H268D, L234F/S267E/N325L, G237F/V266L/S267D and other mutations listed in

WO2011/120134 and WO2011/120135, herein incorporated by reference. *Therapeutic Antibody*

Engineering (by William R. Strohl and Lila M. Strohl, Woodhead Publishing series in Biomedicine No 11, ISBN 1 907568 37 9, Oct 2012) lists mutations on page 283.

[0289] In some embodiments an antibody described herein includes modifications to improve its ability to mediate effector function. Such modifications are known in the art and include afucosylation, or engineering of the affinity of the Fc towards an activating receptor, mainly FCGR3a for ADCC, and towards C1q for CDC. The following Table B summarizes various designs reported in the literature for effector function engineering.

[0290] Methods of producing antibodies with little or no fucose on the Fc glycosylation site (Asn 297 EU numbering) without altering the amino acid sequence are well known in the art. The GlymaX® technology (ProBioGen AG) is based on the introduction of a gene for an enzyme which deflects the cellular pathway of fucose biosynthesis into cells used for antibody production. This prevents the addition of the sugar “fucose” to the N-linked antibody carbohydrate part by antibody-producing cells. (von Horsten et al. (2010) *Glycobiology*. 2010 Dec; 20 (12):1607-18. Another approach to obtaining antibodies with lowered levels of fucosylation can be found in U.S. patent 8,409,572, which teaches selecting cell lines for antibody production for their ability to yield lower levels of fucosylation on antibodies can be fully afucosylated (meaning they contain no detectable fucose) or they can be partially afucosylated, meaning that the isolated antibody contains less than 95%, less than 85%, less than 75%, less than 65%, less than 55%, less than 45%, less than 35%, less than 25%, less than 15% or less than 5% of the amount of fucose normally detected for a similar antibody produced by a mammalian expression system.

[0291] Thus, in one embodiment, an antibody described herein can include a dimeric Fc that comprises one or more amino acid modifications as noted in Table B that confer improved effector function. In another embodiment, the antibody can be afucosylated to improve effector function.

Table B: CH2 domains and effector function engineering

Table B		
Reference	Mutations	Effect
Lu, 2011, Ferrara 2011, Mizushima 2011	Afucosylated	Increased ADCC
Lu, 2011	S298A/E333A/K334A	Increased ADCC
Lu, 2011	S298A/E333A/K334A/K326A	Increased ADCC
Stavenhagen, 2007	F243L/R292P/Y300L/V305I/P396L	Increased ADCC
Nordstrom, 2011	F243L/R292P/Y300L/L235V/P396L	Increased ADCC
Stewart, 2011	F243L	Increased ADCC
Shields, 2001	S298A/E333A/K334A	Increased ADCC
Lazar, 2006	S239D/I332E/A330L	Increased ADCC

Lazar, 2006	S239D/I332E	Increased ADCC
Bowles, 2006	AME-D, not specified mutations	Increased ADCC
Heider, 2011	37.1, mutations not disclosed	Increased ADCC
Moore, 2010	S267E/H268F/S324T	Increased CDC

[0292] Fc modifications reducing FcγR and/or complement binding and/or effector function are known in the art. Recent publications describe strategies that have been used to engineer antibodies with reduced or silenced effector activity (see Strohl, WR (2009), Curr Opin Biotech 20:685-691, and Strohl, WR and Strohl LM, “Antibody Fc engineering for optimal antibody performance” In Therapeutic Antibody Engineering, Cambridge: Woodhead Publishing (2012), pp 225-249). These strategies include reduction of effector function through modification of glycosylation, use of IgG2/IgG4 scaffolds, or the introduction of mutations in the hinge or CH2 regions of the Fc. For example, US Patent Publication No. 2011/0212087 (Strohl), International Patent Publication No. WO 2006/105338 (Xencor), US Patent Publication No. 2012/0225058 (Xencor), US Patent Publication No. 2012/0251531 (Genentech), and Strop et al ((2012) J. Mol. Biol. 420: 204-219) describe specific modifications to reduce FcγR or complement binding to the Fc.

[0293] Specific, non-limiting examples of known amino acid modifications to reduce FcγR or complement binding to the Fc include those identified in the following **Table C**:

Table C: Modifications to reduce FcγR or complement binding to the Fc

Table C	
Company	Mutations
GSK	N297A
Ortho Biotech	L234A/L235A
Protein Design labs	IGG2 V234A/G237A
Wellcome Labs	IGG4 L235A/G237A/E318A
GSK	IGG4 S228P/L236E
Alexion	IGG2/IGG4combo
Merck	IGG2 H268Q/V309L/A330S/A331S
Bristol-Myers	C220S/C226S/C229S/P238S
Seattle Genetics	C226S/C229S/E3233P/L235V/L235A
Amgen	E.coli production, non glyco

Medimune	I.234F/I.235F/P331S
Trubion	Hinge mutant, possibly C226S/P230S

[0294] Methods of producing antibodies with little or no fucose on the Fc glycosylation site (Asn 297 EU numbering) without altering the amino acid sequence are well known in the art. The GlymaxX® technology (ProBioGen AG) is based on the introduction of a gene for an enzyme which deflects the cellular pathway of fucose biosynthesis into cells used for antibody production. This prevents the addition of the sugar “fucose” to the N-linked antibody carbohydrate part by antibody-producing cells. (von Horsten et al. (2010) *Glycobiology*. 2010 Dec; 20 (12):1607-18.) Examples of cell lines capable of producing defucosylated antibody include CHO-DG44 with stable overexpression of the bacterial oxidoreductase GDP-6-deoxy-D-lyxo-4-hexylose reductase (RMD) (see Henning von Horsten et al., *Glycobiol* 2010, 20:1607-1618) or Lec13 CHO cells, which are deficient in protein fucosylation (see Ripka et al., *Arch. Biochem. Biophys.*, 1986, 249:533-545; U.S. Pat. Pub. No. 2003/0157108; WO 2004/056312; each of which is incorporated by reference in its entirety), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene or FUT8 knockout CHO cells (see Yamane-Ohnuki et al., *Biotech. Bioeng.*, 2004, 87: 614-622; Kanda et al., *Biotechnol. Bioeng.*, 2006, 94:680-688; and WO 2003/085107; each of which is incorporated by reference in its entirety). Another approach to obtaining antibodies with lowered levels of fucosylation can be found in U.S. patent 8,409,572, which teaches selecting cell lines for antibody production for their ability to yield lower levels of fucosylation on antibodies

[0295] Examples of cell lines capable of producing defucosylated antibody include CHO-DG44 with stable overexpression of the bacterial oxidoreductase GDP-6-deoxy-D-lyxo-4-hexylose reductase (RMD) (see Henning von Horsten et al., *Glycobiol* 2010, 20:1607-1618) or Lec13 CHO cells, which are deficient in protein fucosylation (see Ripka et al., *Arch. Biochem. Biophys.*, 1986, 249:533-545; U.S. Pat. Pub. No. 2003/0157108; WO 2004/056312; each of which is incorporated by reference in its entirety), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene or FUT8 knockout CHO cells (see Yamane-Ohnuki et al., *Biotech. Bioeng.*, 2004, 87: 614-622; Kanda et al., *Biotechnol. Bioeng.*, 2006, 94:680-688; and WO 2003/085107; each of which is incorporated by reference in its entirety).

[0296] Antibodies can be fully afucosylated (meaning they contain no detectable fucose) or they can be partially afucosylated, meaning that the isolated antibody contains less than 95%, less than 85%, less than 75%, less than 65%, less than 55%, less than 45%, less than 35%, less than 25%, less than 15% or less than 5% of the amount of fucose normally detected for a similar antibody produced by a mammalian expression system.

[0297] In some aspects, an antibody provided herein comprises an IgG1 domain with reduced fucose content at position Asn 297 compared to a naturally occurring IgG1 domain. Such Fc domains are known to have improved ADCC. See Shields et al., *J. Biol. Chem.*, 2002, 277:26733-26740, incorporated by reference in its entirety. In some aspects, such antibodies do not comprise any fucose at position Asn 297. The amount of fucose may be determined using any suitable method, for example as described in WO 2008/077546, incorporated by reference in its entirety.

[0298] In certain embodiments, an antibody provided herein comprises an Fc region with one or more amino acid substitutions which improve ADCC, such as a substitution at one or more of positions 298, 333, and 334 of the Fc region. In some embodiments, an antibody provided herein comprises an Fc region with one or more amino acid substitutions at positions 239, 332, and 330, as described in Lazar et al., *Proc. Natl. Acad. Sci. USA*, 2006, 103:4005-4010, incorporated by reference in its entirety.

[0299] Other illustrative glycosylation variants which may be incorporated into the antibodies provided herein are described, for example, in U.S. Pat. Pub. Nos. 2003/0157108, 2004/0093621, 2003/0157108, 2003/0115614, 2002/0164328, 2004/0093621, 2004/0132140, 2004/0110704, 2004/0110282, 2004/0109865; International Pat. Pub. Nos. 2000/61739, 2001/29246, 2003/085119, 2003/084570, 2005/035586, 2005/035778; 2005/053742, 2002/031140; Okazaki et al., *J. Mol. Biol.*, 2004, 336:1239-1249; and Yamane-Ohnuki et al., *Biotech. Bioeng.*, 2004, 87: 614-622; each of which is incorporated by reference in its entirety.

[0300] In some embodiments, an antibody provided herein comprises an Fc region with at least one galactose residue in the oligosaccharide attached to the Fc region. Such antibody variants may have improved CDC function. Examples of such antibody variants are described, for example, in WO 1997/30087; WO 1998/58964; and WO 1999/22764; each of which is incorporated by reference in its entirety.

[0301] In some embodiments, an antibody provided herein comprises one or more alterations that improves or diminishes C1q binding and/or CDC. See U.S. Pat. No. 6,194,551; WO 99/51642; and Idusogie et al., *J. Immunol.*, 2000, 164:4178-4184; each of which is incorporated by reference in its entirety.

Binding

[0302] The affinity of a molecule X for its partner Y can be represented by the dissociation equilibrium constant (K_D). The kinetic components that contribute to the dissociation equilibrium constant are described in more detail below. Affinity can be measured by common methods known in

the art, including those described herein, such as surface plasmon resonance (SPR) technology (e.g., BIACORE®) or biolayer interferometry (e.g., FORTEBIO®).

[0303] With regard to the binding of an antibody to a target molecule, the terms “bind,” “specific binding,” “specifically binds to,” “specific for,” “selectively binds,” and “selective for” a particular antigen (e.g., a polypeptide target) or an epitope on a particular antigen mean binding that is measurably different from a non-specific or non-selective interaction (e.g., with a non-target molecule). Specific binding can be measured, for example, by measuring binding to a target molecule and comparing it to binding to a non-target molecule. Specific binding can also be determined by competition with a control molecule that mimics the epitope recognized on the target molecule. In that case, specific binding is indicated if the binding of the antibody to the target molecule is competitively inhibited by the control molecule. In some embodiments, the affinity of a fibrin antibody for a non-target molecule is less than about 50% of the affinity for fibrin. In some embodiments, the affinity of a fibrin antibody for a non-target molecule is less than about 40% of the affinity for fibrin. In some embodiments, the affinity of a fibrin antibody for a non-target molecule is less than about 30% of the affinity for fibrin. In some embodiments, the affinity of a fibrin antibody for a non-target molecule is less than about 20% of the affinity for fibrin. In some embodiments, the affinity of a fibrin antibody for a non-target molecule is less than about 10% of the affinity for fibrin. In some embodiments, the affinity of a fibrin antibody for a non-target molecule is less than about 1% of the affinity for fibrin. In some embodiments, the affinity of a fibrin antibody for a non-target molecule is less than about 0.1% of the affinity for fibrin.

[0304] When used herein in the context of two or more antibodies, the term “competes with” or “cross-competes with” indicates that the two or more antibodies compete for binding to an antigen (e.g., fibrin). In one exemplary assay, fibrin is coated on a surface and contacted with a first fibrin antibody, after which a second fibrin antibody is added. In another exemplary assay, a first fibrin antibody is coated on a surface and contacted with fibrin, and then a second fibrin antibody is added. If the presence of the first fibrin antibody reduces binding of the second fibrin antibody, in either assay, then the antibodies compete with each other. The term “competes with” also includes combinations of antibodies where one antibody reduces binding of another antibody, but where no competition is observed when the antibodies are added in the reverse order. However, in some embodiments, the first and second antibodies inhibit binding of each other, regardless of the order in which they are added. In some embodiments, one antibody reduces binding of another antibody to its antigen by at least 25%, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% as measured in a competitive binding assay. A skilled artisan can

select the concentrations of the antibodies used in the competition assays based on the affinities of the antibodies for fibrin and the valency of the antibodies. The assays described in this definition are illustrative, and a skilled artisan can utilize any suitable assay to determine if antibodies compete with each other. Suitable assays are described, for example, in Cox et al., "Immunoassay Methods," in Assay Guidance Manual [Internet], Updated December 24, 2014 (ncbi.nlm.nih.gov/books/NBK92434/; accessed September 29, 2015); Silman et al., Cytometry, 2001, 44:30-37; and Finco et al., J. Pharm. Biomed. Anal., 2011, 54:351-358; each of which is incorporated by reference in its entirety.

[0305] A test antibody competes with a reference antibody if an excess of a test antibody (e.g., at least 2x, 5x, 10x, 20x, or 100x) inhibits or blocks binding of the reference antibody by, e.g., at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% as measured in a competitive binding assay. Antibodies identified by competition assay (competing antibody) include antibodies binding to the same epitope as the reference antibody and antibodies binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antibody for steric hindrance to occur. For example, a second, competing antibody can be identified that competes for binding to fibrin with a first antibody described herein. In certain instances, the second antibody can block or inhibit binding of the first antibody by, e.g., at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% as measured in a competitive binding assay. In certain instances, the second antibody can displace the first antibody by greater than 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99%.

[0306] In some embodiments, an anti- fibrin antibody does not substantially bind myeloid cells present outside of cancer tissue. In some embodiments, an anti- fibrin antibody does not substantially bind stimulatory myeloid cells present in cancer tissue.

[0307] In some embodiments, an anti- fibrin antibody binds to residues γ 377-395 of the fibrin or fibrinogen γ C domain (SEQ ID NO: 31) of human fibrin. The binding epitope includes the residues within the numerical range (e.g., residues 377-395 of fibrin), the beginning residue of each range (e.g., residues 377-394 of human fibrin) and the end residue of each range (e.g., residues 378-395 of human fibrin), or any combination thereof.

[0308] In some embodiments, an antibody provided herein binds human Fibrin with a K_D of less than or equal to about 0.001, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 1.95, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, or 10×10^{-6} M, as measured by Biacore assay. In some embodiments, the K_D of the antibody provided herein is between about 0.001-0.01, 0.01-0.1, 0.01-0.05, 0.05-0.1, 0.1-0.5, 0.5-1, 0.25-0.75, 0.25-0.5, 0.5-0.75, 0.75-1, 0.75-2, 1.1-1.2, 1.2-1.3, 1.3-1.4, 1.4-1.5, 1.5-1.6, 1.6-1.7, 1.7-1.8, 1.8-1.9, 1.9-2, 1-2, 1-

5, 2-7, 3-8, 3-5, 4-6, 5-7, 6-8, 7-9, 7-10, or $5-10 \times 10^{-6}$ M, as measured by Biacore assay. In some embodiments, an antibody provided herein binds human Fibrin with a K_D of less than or equal to about 1×10^{-5} M, 1×10^{-6} M, 1×10^{-7} M, 1×10^{-8} M, or 1×10^{-9} M.

[0309] In some embodiments, the antibody provided herein binds human fibrin with a K_D of less than or equal to about 10, 9, 8, 7, 6, 5, 4.5, 4, 3.5, 3, 2.5, 2, 1.98, 1.95, 1.9, 1.85, 1.8, 1.75, 1.7, 1.65, 1.6, 1.55, 1.50, 1.45, 1.4, 1.3, 1.2, 1.1, 1, 0.9, 0.85, 0.8, 0.75, 0.7, 0.65, 0.6, 0.55, 0.5, 0.45, 0.4, 0.35, 0.3, 0.25, 0.2, 0.15, 0.1, 0.05, 0.01, 0.005, 0.001, 0.0005, or 0.0001×10^{-5} M, or less, as measured by Biacore assay. In some embodiments, the antibody provided herein binds human fibrin with a K_D between 5-3, 4-2, 3-1, 1.9-1.8, 1.8-1.7, 1.7-1.6, 1.6-1.5, 1.9-1.5, 1.5-1, 1-0.8, 1-0.5, 0.9-0.6, 0.7-0.4, 0.6-0.2, 0.5-0.3, 0.3-0.2, 0.2-0.1, 0.1-0.01, 0.01-0.001, or $0.001-0.0001 \times 10^{-5}$ M as measured by Biacore assay. In some embodiments, the antibody provided herein binds human fibrin with a K_a of less than or equal to about 10, 9.56, 9.5, 9.0, 8.88, 8.84, 8.5, 8, 7.5, 7.32, 7, 6.5, 6, 5.5, 5, 4.5, 4, 3.5, 3, 2.5, 2, 1.5, or 1×10^{-4} (1/s), or less, as measured by Biacore assay. In some embodiments, the antibody provided herein binds human fibrin with a K_a between 7-10, 7-8, 8-9, 9-10, 7-7.5, 7.5-8, 8.-8.5, 8.5-9, 9-9.5, or $9.5-10 \times 10^{-4}$ (1/s) as measured by Biacore assay. In some embodiments, the antibody provided herein binds human fibrin with a K_a of greater than or equal to about 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 45, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 7, 8, 9, or 10×10^5 (1/Ms), or more, as measured by Biacore assay. In some embodiments, the antibody provided herein binds human FIBRIN with a K_a between 4-7, 4-4.5, 4.5-5, 5-5.5, 5.5-6, 6-6.5, or 6.5-7, 7-8, 8-9, or $9-10 \times 10^5$ (1/Ms) as measured by Biacore assay.

Function

[00203] “Effector functions” refer to those biological activities mediated by the Fc region of an antibody, which activities may vary depending on the antibody isotype. Examples of antibody effector functions include receptor ligand blocking, agonism, or antagonism, C1q binding to activate complement dependent cytotoxicity (CDC), Fc receptor binding to activate antibody-dependent cellular cytotoxicity (ADCC), and antibody dependent cellular phagocytosis (ADCP). In some embodiments, the effector function of the fibrin antibody described herein is antagonism and blocks Mac-1 receptor binding to fibrin.

Pharmaceutical compositions

[00204] The present application provides compositions comprising the antibodies including pharmaceutical compositions comprising any one or more of the antibodies described herein with one or more pharmaceutically acceptable excipients. In some embodiments the composition is sterile. The pharmaceutical compositions generally comprise an effective amount of an antibody.

[00205] These compositions can comprise, in addition to one or more of the antibodies disclosed herein, a pharmaceutically acceptable excipient, carrier, buffer, stabilizer or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material can depend on the route of administration, e.g. oral, intravenous, cutaneous or subcutaneous, nasal, intramuscular, intraperitoneal routes.

[00206] Pharmaceutical compositions for oral administration can be in tablet, capsule, powder or liquid form. A tablet can include a solid carrier such as gelatin or an adjuvant. Liquid pharmaceutical compositions generally include a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol can be included.

[00207] For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives can be included, as required.

[00208] The anti-fibrin antibody that is to be given to an individual, administration is preferably in a "therapeutically effective amount" or "prophylactically effective amount" (as the case can be, although prophylaxis can be considered therapy), this being sufficient to show benefit to the individual. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of protein aggregation disease being treated. Prescription of treatment, e.g. decisions on dosage etc., is within the responsibility of general practitioners and other medical doctors, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 16th edition, Osol, A. (ed), 1980.

[00209] A composition can be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated.

Methods

Methods of Preparation

[0210] Antibodies described herein can be produced using recombinant methods and compositions, e.g., as described in U.S. Pat. No. 4,816,567. In one embodiment, isolated nucleic acid encoding an

antibody described herein is provided. Such nucleic acid may encode an amino acid sequence comprising the VL and/or an amino acid sequence comprising the VH of the antibody (e.g., the light and/or heavy chains of the antibody) or an amino acid sequence comprising the VHH of a single domain antibody. In a further embodiment, one or more vectors (e.g., expression vectors) comprising such nucleic acid are provided. In one embodiment, the nucleic acid is provided in a multicistronic vector. In a further embodiment, a host cell comprising such nucleic acid is provided. In one such embodiment, a host cell comprises (e.g., has been transformed with): (1) a vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and an amino acid sequence comprising the VH of the antigen-binding polypeptide construct, or (2) a first vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antigen-binding polypeptide construct and a second vector comprising a nucleic acid that encodes an amino acid sequence comprising the VH of the antigen-binding polypeptide construct. In one embodiment, the host cell is eukaryotic, e.g. a Chinese Hamster Ovary (CHO) cell, or human embryonic kidney (HEK) cell, or lymphoid cell (e.g., Y0, NS0, Sp20 cell). In one embodiment, a method of making an antibody is provided, wherein the method comprises culturing a host cell comprising nucleic acid encoding the antibody, as provided above, under conditions suitable for expression of the antibody, and optionally recovering the antibody from the host cell (or host cell culture medium).

[0211] For recombinant production of the antibody, nucleic acid encoding an antibody, e.g., as described above, is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

[0212] When a heteromultimer or variant thereof is recombinantly produced by the host cells, the protein in certain embodiments is present at about 30%, about 25%, about 20%, about 15%, about 10%, about 5%, about 4%, about 3%, about 2%, or about 1% or less of the dry weight of the cells. When the heteromultimer or variant thereof is recombinantly produced by the host cells, the protein, in certain embodiments, is present in the culture medium at about 5 g/L, about 4 g/L, about 3 g/L, about 2 g/L, about 1 g/L, about 750 mg/L, about 500 mg/L, about 250 mg/L, about 100 mg/L, about 50 mg/L, about 10 mg/L, or about 1 mg/L or less of the dry weight of the cells. In certain embodiments, “substantially purified” heteromultimer produced by the methods described herein, has a purity level of at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, specifically, a purity level of at least about 75%, 80%, 85%, and more specifically, a purity level of at

least about 90%, a purity level of at least about 95%, a purity level of at least about 99% or greater as determined by appropriate methods such as SDS/PAGE analysis, RP-HPLC, SEC, and capillary electrophoresis.

[0213] Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells described herein.

[0214] Recombinant host cells or host cells are cells that include an exogenous polynucleotide, regardless of the method used for insertion, for example, direct uptake, transduction, f-mating, or other methods known in the art to create recombinant host cells. The exogenous polynucleotide may be maintained as a nonintegrated vector, for example, a plasmid, or alternatively, may be integrated into the host genome. Host cells can include CHO, derivatives of CHO, NS0, Sp2O, CV-1, VERO-76, HeLa, HepG2, Per.C6, or BHK.

[0215] For example, antibody may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria, see, e.g., U.S. Pat. Nos. 5,648,237, 5,789,199, and 5,840,523. (See also Charlton, *Methods in Molecular Biology*, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, N.J., 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*.) After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

[0216] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors, including fungi and yeast strains whose glycosylation pathways have been “humanized,” resulting in the production of an antibody with a partially or fully human glycosylation pattern. See Gerngross, *Nat. Biotech.* 22:1409-1414 (2004), and Li et al., *Nat. Biotech.* 24:210-215 (2006).

[0217] Suitable host cells for the expression of glycosylated antibodies are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of *Spodoptera frugiperda* cells.

[0218] Plant cell cultures can also be utilized as hosts. See, e.g., U.S. Pat. Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIES™ technology for producing antibodies in transgenic plants).

[0219] Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, e.g., in Graham et al., *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells

(BHK); mouse sertoli cells (TM4 cells as described, e.g., in Mather, Biol. Reprod. 23:243-251 (1980)); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, e.g., in Mather et al., Annals N.Y. Acad. Sci. 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR- CHO cells (Urlaub et al., Proc. Natl. Acad. Sci. USA 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, e.g., Yazaki and Wu, Methods in Molecular Biology, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, N.J.), pp. 255-268 (2003).

[0220] In one embodiment, the antibodies described herein are produced in stable mammalian cells, by a method comprising: transfecting at least one stable mammalian cell with: nucleic acid encoding the antibody, in a predetermined ratio; and expressing the nucleic acid in the at least one mammalian cell. In some embodiments, the predetermined ratio of nucleic acid is determined in transient transfection experiments to determine the relative ratio of input nucleic acids that results in the highest percentage of the antibody in the expressed product.

[0221] In some embodiments, is the method of producing an antibody in stable mammalian cells as described herein wherein the expression product of the at least one stable mammalian cell comprises a larger percentage of the desired glycosylated antibody as compared to the monomeric heavy or light chain polypeptides, or other antibodies.

[0222] In some embodiments, is the method of producing a glycosylated antibody in stable mammalian cells described herein, said method comprising identifying and purifying the desired glycosylated antibody. In some embodiments, the said identification is by one or both of liquid chromatography and mass spectrometry.

[0223] If required, the antibodies can be purified or isolated after expression. Proteins may be isolated or purified in a variety of ways known to those skilled in the art. Standard purification methods include chromatographic techniques, including ion exchange, hydrophobic interaction, affinity, sizing or gel filtration, and reversed-phase, carried out at atmospheric pressure or at high pressure using systems such as FPLC and HPLC. Purification methods also include electrophoretic, immunological, precipitation, dialysis, and chromatofocusing techniques. Ultrafiltration and diafiltration techniques, in conjunction with protein concentration, are also useful. As is well known in the art, a variety of natural proteins bind Fc and antibodies, and these proteins can find use in the present invention for purification of antibodies. For example, the bacterial proteins A and G bind to

the Fc region. Likewise, the bacterial protein L binds to the Fab region of some antibodies. Purification can often be enabled by a particular fusion partner. For example, antibodies may be purified using glutathione resin if a GST fusion is employed, Ni²⁺ affinity chromatography if a His-tag is employed or immobilized anti-flag antibody if a flag-tag is used. For general guidance in suitable purification techniques, see, e.g. incorporated entirely by reference Protein Purification: Principles and Practice, 3rd Ed., Scopes, Springer-Verlag, NY, 1994, incorporated entirely by reference. The degree of purification necessary will vary depending on the use of the antibodies. In some instances, no purification is necessary.

[0224] In certain embodiments, the antibodies are purified using Anion Exchange Chromatography including, but not limited to, chromatography on Q-sepharose, DEAE sepharose, poros HQ, poros DEAF, Toyopearl Q, Toyopearl QAE, Toyopearl DEAE, Resource/Source Q and DEAE, Fractogel Q and DEAE columns.

[0225] In specific embodiments, the proteins described herein are purified using Cation Exchange Chromatography including, but not limited to, SP-sepharose, CM sepharose, poros HS, poros CM, Toyopearl SP, Toyopearl CM, Resource/Source S and CM, Fractogel S and CM columns and their equivalents and comparables.

[0226] In addition, antibodies described herein can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W. H. Freeman & Co., N.Y and Hunkapiller et al., Nature, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4diaminobutyric acid, alpha-amino isobutyric acid, 4aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, alanine, fluoro-amino acids, designer amino acids such as methyl amino acids, C-methyl amino acids, N-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

Methods of Use

[0227] In an aspect, the present application provides methods of contacting fibrin with an anti-fibrin antibody, such as a human or humanized antibody, which results in inhibition of microglial adhesion to the fibrin or fibrinogen γ C domain.

[00228] In an aspect, the present application provides methods of using the isolated anti-fibrin antibodies described herein for treatment of a degenerative disorder of the nervous system. In certain aspects, described herein is a method for treating a degenerative disorder of the nervous system, the method comprising administering to a mammalian subject a therapeutically effective amount of an anti-fibrin antibody or pharmaceutical composition comprising an anti-fibrin antibody described herein. In certain embodiments, the present application provides methods of treating a degenerative disorder of the nervous system selected from the group consisting of: multiple sclerosis, spinal cord injury, stroke, and Alzheimer's Disease.

[00229] In certain aspects, described herein are methods for treating a pathology associated with Mac-1 binding to fibrin or Mac-1 binding with fibrinogen, the method comprising administering to a mammalian subject a therapeutically effective amount an isolated anti-fibrin antibody or a pharmaceutical composition comprising an isolated anti-fibrin antibody described herein.

[00230] In certain aspects, described herein are methods of inhibiting microglia activation, the method comprising administering to a mammalian subject a therapeutically effective amount an isolated anti-fibrin antibody or a pharmaceutical composition comprising an isolated antibody described herein.

[00231] In certain aspects, described herein is a method of preventing a degenerative disorder of the nervous system, the method comprising administering to a mammalian subject a therapeutically effective amount an isolated anti-fibrin antibody or a pharmaceutical composition comprising an isolated anti-fibrin antibody described herein. In certain embodiments, the present application provides methods of preventing a degenerative disorder of the nervous system selected from the group consisting of: multiple sclerosis, spinal cord injury, stroke, and Alzheimer's Disease.

[00232] In certain aspects, described herein are methods of treating or preventing colitis, comprising administering to a mammalian subject a therapeutically effective amount an isolated anti-fibrin antibody or a pharmaceutical composition comprising an isolated anti-fibrin antibody described herein.

[00233] In certain aspects, , described herein are methods of treating or preventing an inflammatory condition of the eye comprising administering to a mammalian subject a therapeutically effective amount an isolated anti-fibrin antibody or a pharmaceutical composition comprising an isolated anti-fibrin antibody described herein. In certain embodiments, the inflammatory condition of the eye is uveitis.

Methods of Administration

[0232] In some embodiments, the methods provided herein are useful for the treatment of a degenerative nervous system disorder in an individual. In an embodiment, the individual is a human and the antibody is a fibrin antibody described herein.

[0233] In some embodiments, an antibody is administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, intravitreally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. An effective amount of an anti-fibrin antibody may be administered for the treatment of cancer. The appropriate dosage of the anti-fibrin antibody may be determined based on the type of cancer to be treated, the type of the anti-fibrin antibody, the severity and course of the cancer, the clinical condition of the individual, the individual's clinical history and response to the treatment, and the discretion of the attending physician.

[00234] In some embodiments, an antibody provided herein is administered with at least one additional therapeutic agent. Any suitable additional therapeutic or immunotherapeutic agent may be administered with an antibody provided herein. Additional therapeutic agents include agents that are used to treat or prevent a degenerative disorder of the nervous system selected from the group consisting of: multiple sclerosis, spinal cord injury, stroke, and Alzheimer's Disease.

[00235] The additional therapeutic agent can be administered by any suitable means. In some embodiments, an antibody provided herein and the additional therapeutic agent are included in the same pharmaceutical composition. In some embodiments, an antibody provided herein and the additional therapeutic agent are included in different pharmaceutical compositions.

[00236] In embodiments where an antibody provided herein and the additional therapeutic agent are included in different pharmaceutical compositions, administration of the antibody can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent. In some embodiments, administration of an antibody provided herein and the additional therapeutic agent occur within about one month of each other. In some embodiments, administration of an antibody provided herein and the additional therapeutic agent occur within about one week of each other. In some embodiments, administration of an antibody provided herein and the additional therapeutic agent occur within about one day of each other. In some embodiments, administration of an antibody provided herein and the additional therapeutic agent occur within about twelve hours of each other. In some embodiments, administration of an antibody provided herein and the additional therapeutic agent occur within about one hour of each other.

Kits and Articles of Manufacture

[0237] The present application provides kits comprising any one or more of the antibody compositions described herein. In some embodiments, the kits further contain a component selected from any of secondary antibodies, reagents for immunohistochemistry analysis, pharmaceutically acceptable excipient and instruction manual and any combination thereof. In one specific embodiment, the kit comprises a pharmaceutical composition comprising any one or more of the antibody compositions described herein, with one or more pharmaceutically acceptable excipients.

[0238] The present application also provides articles of manufacture comprising any one of the antibody compositions or kits described herein. Examples of an article of manufacture include vials (including sealed vials).

EXAMPLES

[00239] Below are examples of specific embodiments for carrying out the present invention. The examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental error and deviation should, of course, be allowed for.

[00240] The practice of the present invention will employ, unless otherwise indicated, conventional methods of protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art. Such techniques are explained fully in the literature. See, e.g., T.E. Creighton, *Proteins: Structures and Molecular Properties* (W.H. Freeman and Company, 1993); A.L. Lehninger, *Biochemistry* (Worth Publishers, Inc., current addition); Sambrook, et al., *Molecular Cloning: A Laboratory Manual* (2nd Edition, 1989); *Methods In Enzymology* (S. Colowick and N. Kaplan eds., Academic Press, Inc.); *Remington's Pharmaceutical Sciences*, 18th Edition (Easton, Pennsylvania: Mack Publishing Company, 1990); Carey and Sundberg *Advanced Organic Chemistry 3rd Ed.* (Plenum Press) Vols A and B(1992).

Materials and Methods

[00241] Antigens were biotinylated using the EZ-Link Sulfo-NHS-Biotinylation Kit from Pierce. Goat F(ab')₂ anti-human kappa-FITC (LC-FITC), ExtrAvidin-PE (EA-PE) and Streptavidin-AF633 (SA-633) were obtained from Southern Biotech, Sigma, and Molecular Probes, respectively. Goat anti-human IgG-PE (Human-PE) was obtained from Southern Biotech. Anti-Mouse APC was obtained from Jackson ImmunoResearch.

Example 1: Humanization of anti-fibrin antibodies

[00242] The process of humanization modifies binding domains from a non-human antibody increasing similarity to human binding domains. Typically, a non-human antibody is humanized to reduce immunogenicity to humans, while retaining the specificity and affinity of the parental non-human antibody. Generally, a humanized antibody comprises one or more variable domains in which CDRs, (or portions thereof) are derived from a non-human antibody, and FRs (or portions thereof) are derived from human antibody sequences. A humanized antibody will also comprise at least a portion of a human constant region. In some embodiments, some FR residues in a humanized antibody are substituted with corresponding residues from a non-human antibody (e.g., the antibody from which the CDR residues are derived), e.g., to restore or improve antibody specificity, affinity, stability, or developability profile.

[00243] Humanized antibodies and methods of making them are reviewed, e.g., in Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008), and are further described, e.g., in Riechmann et al., *Nature* 332:323-329 (1988); Queen et al., *Proc. Nat'l Acad. Sci. USA* 86:10029-10033 (1989); U.S. Pat. Nos. 5,821,337, 7,527,791, 6,982,321, and 7,087,409; Kashmiri et al., *Methods* 36:25-34 (2005) (describing specificity determining region (SDR) grafting); Padlan, *Mol. Immunol.* 28:489-498 (1991) (describing “resurfacing”); Dall’Acqua et al., *Methods* 36:43-60 (2005) (describing “FR shuffling”); and Osbourn et al., *Methods* 36:61-68 (2005) and Klimka et al., *Br. J. Cancer*, 83:252-260 (2000) (describing the “guided selection” approach to FR shuffling).

[00244] Human framework regions that may be used for humanization include but are not limited to: framework regions selected using the “best-fit” method (see, e.g., Sims et al. *J. Immunol.* 151:2296 (1993)); framework regions derived from the consensus sequence of human antibodies of a particular subgroup of light or heavy chain variable regions (see, e.g., Carter et al. *Proc. Natl. Acad. Sci. USA*, 89:4285 (1992); and Presta et al. *J. Immunol.*, 151:2623 (1993)); human mature (somatically mutated) framework regions or human germline framework regions (see, e.g., Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008)); and framework regions derived from screening FR libraries (see, e.g., Baca et al., *J. Biol. Chem.* 272:10678-10684 (1997) and Rosok et al., *J. Biol. Chem.* 271:22611-22618 (1996)).

Humanization of 5B8

[00245] Humanization of a Fibrin antibody (5B8) was conducted by characterizing a panel of humanization designs produced in yeast. In brief, the designs were generated by grafting CDR mouse sequences into human framework sequences that had *in silico* been predicted to be the most compatible to the original mouse frameworks. The following combinations were produced in yeast

and characterized for binding to human fibrinogen P2 peptide antigen: Based on 5B8, 27 antibodies representing combinations of 9 humanized VH and 3 humanized Vκ.

Antibody Optimization

[00246] Optimization of the humanized antibodies was performed by introducing diversities into the heavy chain and light chain variable regions as described below.

[00247] Library generation: Oligonucleotides were ordered from IDT which comprised either the CDRH1, CDRH2, or CDRH3 as well as a flanking region on either side of the CDR. Amino acid positions in the CDRs were variegated via NNK diversity introduced into the CDR oligos. The DNA of the HC (heavy chain) variable region was then DNase treated to create fragments of 50-200 bps in size. The CDRH1, CDRH2, and CDRH3 oligos were then recombined with the DNase treated HC variable region via overlap extension PCR to incorporate the CDR diversity oligos into the HC variable region sequence. The library was then created by transforming this diversified HC variable sequence and the heavy chain expression vector into yeast already containing the light chain plasmid of the parent. A similar process was performed to introduce diversity in the CDRL1, CDRL2 and CDRL3. Oligonucleotides were ordered from IDT with diversity in the CDRL1, CDRL2 and CDRL3, and incorporated into diversified light chain (LC) variable regions as described for the CDRH1, CDRH2, CDRH3 libraries. These diversified LC variable regions and the light chain expression vector were transformed into yeast already containing the heavy chain plasmid of the parent. An additional set of libraries were built focusing diversity exclusively within the CDRH3. Walking singlet diversity was introduced into the CDRH3 by overlap extension PCR between VH FR1 through FR3 and an oligonucleotide with diversity in the CDRH3.

[00248] Selections were performed by using FACS sorting for three rounds. Approximately 2×10^7 yeast were pelleted, washed three times with wash buffer, and incubated at 30°C with either an affinity pressure using human fibrinogen P2 peptide antigen or with a poly-specificity depletion reagent (PSR) to remove non-specific antibodies from the selection. For this selection the affinity pressure was applied by preincubating the antigen with parental IgG and then applying that precomplexed mixture to the yeast library for a length of time which would allow the selection to reach an equilibrium. For the PSR depletion the libraries were incubated with a 1:10 dilution of biotinylated PSR reagent as previously described (see Y. Xu et al, *PEDS* 26.10, 663-70 (2013).) Yeast were then washed twice with wash buffer and stained with LC-FITC (diluted 1:100) and either SA-633 (diluted 1:500), EAPE (diluted 1:50), or anti-mouse APC (diluted 1:500) secondary reagents for 15 min at 4°C. After washing twice with wash buffer, the cell pellets were resuspended in 0.3 mL wash buffer and transferred to strainer-capped sort tubes. Sorting was performed using a FACS ARIA

sorter (BD Biosciences) and sort gates were determined to select for antibodies with desired characteristics. Four selection rounds were completed. After the final round of sorting, yeast were plated and individual colonies were picked for characterization. Figure 1 shows results of first three rounds of selection of a single antibody library from one parental antibody and increased affinity of antibodies to fibrin P2 gamma peptide after each round of maturation.

Antibody production and purification

[00249] Yeast clones were grown to saturation and then induced for 48 h at 30°C with shaking. After induction, yeast cells were pelleted and the supernatants were harvested for purification. IgGs were purified using a Protein A column and eluted with acetic acid, pH 3.5. Fab fragments were generated by papain digestion and purified over CaptureSelect (Life Technologies).

Example 2: Characterization and Affinity Maturation of Humanized Antibody Clones

[00250] Enzyme-linked immunosorbent assays (ELISA) were performed with the select humanized antibody clones and the fibrin P2 peptide (Figure 2A), fibrinogen (Figure 2B) and Fibrin (Figure 2C). A= clone 60143; B= clone 61278; C= clone 61278(duplicate); D= parental antibody.

[00251] These results confirm that the affinity matured humanized antibody clones bind to fibrin P2 peptide and fibrin with improved affinity compared to the parental humanized antibody.

[00252] To evaluate if the affinity matured antibody clones affected fibrin polymerization or lysis, clot lysis assays were performed demonstrating clot lysis time of samples in the presence of variant humanized antibodies (Figure 3). A= clone 56666; B= clone 56657; C= clone 60143; D=clone 60181; E=clone 60175; F=clone 60163; G=clone 60173; H=clone 60184; I=clone 60141; J=clone 60179; K=clone 60140; L=clone 60183. The clot lysis assay was performed by preparing two mixtures: mixture 1 comprising 133 nM antibody, 2 uM fibrinogen was prepared in 96 well plate, centrifuged at 55 rpm and incubated for 0.5 h at 37 degrees C, and mixture 2 comprising 20 nM plasminogen, 0.1 U thrombin, 4 mM CaCl₂ and 1 nM tPA was prepared and transferred to the plate. Clot lysis reactions were started immediately after Mixture 2 is transferred to the well. Progress of the reaction was measured at 350 nm. Each plate contained 4 controls: buffer blank without Thrombin-tPA-CaCl₂ mix, Buffer blank, 100 uM GPRP (polymerization inhibitor), and 10 uM EACA (lysis inhibitor).

[00253] The clot lysis time of all tested antibody clones was not significantly change compared to the parental humanized antibody or isotype control antibody (Figure 3).

[00254] These results confirm that the affinity matured humanized antibody clones do not affect fibrin polymerization or fibrin lysis.

ForteBio K_D measurements

[00255] ForteBio affinity measurements were performed on an Octet RED384 generally as previously described (see Estep et al, High throughput solution-based measurement of antibody-antigen affinity and epitope binning. *Mabs* 5(2), 270-278 (2013)). Briefly, ForteBio affinity measurements were performed by loading IgGs on-line onto AHC sensors. Sensors were equilibrated off-line in assay buffer for 30 min and then monitored on-line for 60 seconds for baseline establishment. Sensors with loaded IgGs were exposed to 100 nM antigen for 3 minutes, and afterwards were transferred to assay buffer for 3 min for off-rate measurement. For monovalent affinity assessment Fabs were used instead of IgGs. For this assessment the unbiotinylated Fc fusion antigen was loaded on-line onto AHC or AMC sensors. Sensors were equilibrated off-line in assay buffer for 30 min and then monitored on-line for 60 seconds for baseline establishment. Sensors with loaded antigen were exposed to 100 nM Fab for 3 minutes, and afterwards they were transferred to assay buffer for 3 min for off-rate measurement. All kinetics were analyzed using the 1:1 binding model.

[00256] Figure 4 shows results of ForteBio K_D measurements with either N-terminally biotinylated fibrin P2 peptide conjugated to IgG in solution (100 nM) or FAB (monovalent) in solution (100 nM). Figure 5 shows results of octet Fab in solution (100nM) binding to N-terminally biotinylated fibrin P2 peptide.

[00257] These results show that the affinity matured humanized antibody clones have improved binding affinity to Fibrin P2 gamma peptide compared to the parental humanized antibodies.

PSR Binding Assay

[00258] The PSR assay was done as previously described (see Xu Y, et al. (2013) Addressing polyspecificity of antibodies selected from an in vitro yeast presentation system: A FACS-based, high-throughput selection and analytical tool. *Protein Eng Des Sel* **26(10)**:663–670). In short, soluble membrane proteins were prepared from CHO cells. The enriched membrane fraction was biotinylated using NHS-LCBiotin (Pierce, Thermo Fisher). This polyspecificity reagent was incubated with IgG-presenting yeast, followed by washing. Then secondary labeling mix (Extravidin-R-PE, anti-human LC-FITC, and propidium iodide) was added to the mixture. Samples were analyzed on a FACSCanto II analyzer (BD Biosciences) using an HTS sample injector. Flow cytometry data were analyzed for mean fluorescence intensity (MFI) in the R-PE channel to assess nonspecific binding. MFI values were normalized from 0 to 1 based on three reference antibodies exhibiting low, medium, and high PSR MFI values.

Dynamic Scanning Fluorimetry

[00259] 10 uL of 20x Sypro Orange is added to 20 uL of 0.2-1mg/mL mAb or Fab solution. A RT-PCR instrument (BioRad CFX96 RT PCR) is used to ramp the sample plate temperature from 40 to 95 C at 0.5C increment, with 2min equilibrate at each temperature. The negative of first derivative for the raw data is used to extract T_m.

AC-SINS

[00260] The AC-SINS assay was performed as described previously (see Liu Y, et al. (2014) High-throughput screening for developability during early-stage antibody discovery using self-interaction nanoparticle spectroscopy. *MAbs* **6(2)**:483–492). In short, gold nanoparticles (Ted Pella Inc.) were coated with 80% capturing anti-human goat IgG Fc (Jackson ImmunoResearch) and 20% with polyclonal goat nonspecific antibody (Jackson ImmunoResearch). The antibodies of interest were then incubated with the particles for 2 h and the wavelength shift was measured using Molecular Devices SpectraMax M2 with SoftMax Pro6 software. The self-interacting clones show a higher wavelength shift away from the PBS sample.

HIC (Hydrophobic Interaction Chromatography)

[00261] The methodology for this assay was described previously (see Estep P, et al. (2015) An alternative assay to hydrophobic interaction chromatography for high-throughput characterization of monoclonal antibodies. *MAbs* **7(3)**:553–561). In brief, 5 µg IgG samples (1 mg/mL) were spiked in with a mobile phase A solution (1.8 M ammonium sulfate and 0.1 M sodium phosphate at pH 6.5) to achieve a final ammonium sulfate concentration of about 1 M before analysis. A Sepax Proteomix HIC butyl-NP5 column was used with a linear gradient of mobile phase A and mobile phase B solution (0.1 M sodium phosphate, pH 6.5) over 20 min at a flow rate of 1 mL/min with UV absorbance monitoring at 280 nm.

Example 3: Therapeutic Treatment of Fibrinogen-Induced Encephalomyelitis (FIE)

[00262] The ability of the humanized anti-fibrin antibodies to therapeutically inhibit microglia activation and macrophage infiltration (Figure 6) in a fibrinogen-induced encephalomyelitis (FIE) mouse model was then assessed. To induced FIE, mice were anaesthetized with avertin and placed in a stereotactic apparatus. Plasminogen-free fibrinogen was dissolved in endotoxin-free distilled water, diluted to 5 mg/ml with ACSF (artificial cerebral spinal fluid). Fibrinogen (1 µl of 5 mg/ml) was injected at a rate of 0.3 µl/min with a 10-µl Hamilton syringe attached to a 33 gauge needle into the brain at coordinates: anteroposterior, −1.0 mm; mediolateral, −0.7 mm; dorsoventral, −1.325 mm from the bregma, according to Paxinos and Watson.

[00263] For prophylactic intracerebroventricular (i.c.v.) injections, 10 ug of antibodies were delivered (at a rate of 0.3 µl/min) with a 10-µl syringe attached to a 33 gauge needle into the cerebral

ventricle (anteroposterior, −2.0 mm; mediolateral, 0 mm, dorsoventral, −2.0 mm) 30 min before fibrinogen injection. For prophylactic intravenous (i.v.) injections, antibodies were injected retro-orbitally with a 0.3 mL 29 g insulin syringe 1 h before fibrinogen injection.

[00264] Stereotaxic fibrinogen was injected into the corpus callosum to induce encephalomyelitis. A total of 78 mice, separated into 13 groups: n = 6 mice per group were then injected i.v. with anti-fibrin humanized antibodies at either 10 mg/kg or 30 mg/kg. Brain tissue harvesting and preparation was performed three days post-injection. Sample exclusion: 5 mice; found dead at day 1 post-surgery (C 10 mg/kg, n = 1) and day 2 post-surgery (B 10 mg/kg, n = 1; D 10 mg/kg, n = 1). Wrong site injection (B 10 mg/kg, n = 1; D 10 mg/kg, n = 1). Blinding & Quantification: all FIE experiments, image collection and quantification performed in a blinded manner. Immunohistochemistry (IHC) and quantification was performed as follows: 73 mice samples were included for IHC and quantification. Coronal sections (30 μ m) were prepared on the Cryostat. Tissues were stained with Iba-1 (microglia marker, at a dilution of 1:750) and Mac-2 (macrophage infiltration marker, at a dilution of 1:750). The immunoreactivity of Iba-1 (Iba-1+ area) and Mac-2 (Mac-2+ area) was then calculated. A decrease in both microglia and macrophages were detected in tissues from mice treated with the affinity matured humanized anti-fibrin antibody clones at either 10 mg/kg or 30 mg/kg.

[00265] These results show the humanized antibody variants described herein can therapeutically reduce microglia and macrophage infiltration of mice with FIE.

Example 4: Prophylactic Treatment of Relapsing–Remitting Experimental autoimmune encephalomyelitis (EAE)

[00266] The ability of the humanized anti-fibrin antibodies to prophylactically treat Relapsing–Remitting EAE induced by the epitope of amino acids 139–151 of proteolipid protein (PLP) ('PLP139–151 EAE') was assessed. EAE was induced in 8-9 week old female SJL/J mice by subcutaneous immunization with 15 μ g PLP139-151 in complete Freund's adjuvant supplemented with 400 μ g of heat-inactivated *Mycobacterium tuberculosis* H37Ra (Day 0). 2 days after immunization, mice are injected with 5 ng pertussis toxin via IP administration. Antibodies were administered at 0.2, 1, or 5 mg/kg IP prophylactically twice per week starting on day 0. Dexamethasone (0.5 mg/kg) was administered IP daily as a positive control. Experimental Design: 6 groups: n = 10 mice per group, a total of 60 mice. Dose regimen: Dexamethasone (5 mg/kg, daily), humanized anti-fibrin antibodies (A, B, C, D_5 mg/kg, every 3 days). EAE disability scores were monitored daily up to the end of the study. The study was terminated 3 days post peak-EAE at around day 14-16 of the study and spinal cords were collected for histopathological analysis.

[00267] Sample exclusion: 3 mice; found dead at day 12 (antibody B, n = 1), day 15 (antibody C, n = 1), or day 16 (antibody A, n = 1). Blinding & Quantification: All EAE experiments (antibody

treatment and clinical score) were performed in a blinded manner. 57 spinal cord samples were prepared for tissue processing.

[00268] Clinical score of PLP EAE was assessed in mice that were prophylactically injected with antibodies (5 mg/kg i.p. every 3 days) (Figure 7). The clinical score of mice that had been injected with anti-fibrin humanized antibody was reduced compared to control mice injected with PBS or IgG1 alone. Time to onset of disease was also assessed (Figure 8). There were no mice with paralysis that had been injected with anti-fibrin humanized antibody compared to control mice injected with PBS, IgG1, or dexamethasone alone which had between 25% and over 50% of mice with paralysis (Figure 8). Figure 9 shows clinical score of mice that were subjected to prophylactic injection of PBS alone, dexamethasone, antibody clone 6043 (left) or control antibody human IgG1 (right). Figure 10 shows the proportion of paralyzed mice (complete paralysis- left) or (partial hindlimb paralysis- right) that were subjected to prophylactic injection of PBS alone, dexamethasone (dexa), antibody clone 6043 (at the indicated concentrations; 5= 5 mg/kg, 1= 1 mg/kg and 0.2=0.2 mg/kg) or control antibody human IgG1 (5 mg/kg).

[00269] These results show that the anti-fibrin humanized antibody is effective for prophylactic treatment of encephalomyelitis.

Example 5: Humanized anti-fibrin antibodies reduce fibrin-induced IL-12 expression in BMDM cells

[00270] The ability of the affinity matured humanized anti-fibrin antibodies to alter gene expression of Interleukin (IL)-12b in bone marrow derived macrophage (BMDM) cell lines was assessed (Figures 11-13). Cell culture plates with fibrin-coated wells were pre-incubated with humanized anti-fibrin antibodies for 2 h prior to plating BMDM cells. The cells were incubated with the humanized anti-fibrin antibodies or isotype control, fibrinogen, thrombin and CaCl₂ for six hours and then cells were harvested and RNA isolated for gene expression analysis (Figure 11). Cells incubated with 50 ug/mL isotype control exhibited over a 30 fold increase in IL-12b expression, whereas cells incubated with antibody clones 60143 and 61278 at a concentration of 50 ug/mL, exhibited between 15 and 20 fold increase in IL-12b expression (Figure 10). In another experiment, cells incubated with 10 ug/mL isotype control exhibited about a 55 fold increase in IL-12b expression, whereas cells incubated with antibody clones 60143 and 61278 at a concentration of 10 ug/mL, exhibited between about 20 and 45 fold increase in IL-12b expression (Figure 12). The fold change in IL-12b expression also was reduced as the concentration of antibody clone 60143 and 61278 were increased (Figure 13).

[00271] These results confirm that fibrin induced IL-12b expression is reduced upon anti-fibrin antibody blockade in bone marrow derived macrophages.

Example 6: Treatment of neurodegenerative disease

[00272] The purified humanized antibody variants described herein are formulated into a pharmaceutical composition to be administered to patients for the treatment of a neurodegenerative disease (e.g., multiple sclerosis or Alzheimer's Disease). The pharmaceutical composition comprising a humanized antibody variant described herein is administered at a dose sufficient to effectively reduce the symptoms of the neurodegenerative disease. The pharmaceutical composition is well tolerated and does not induce significant harmful adverse effects in the patient.

Example 7: Humanized antibody variant for treatment of colitis

[00273] The humanized antibody variants were investigated the ability to treat colitis in a mouse model of colitis (Figure 14). To initiate dextran sodium sulfate (DSS) induced colitis treatment, 8–10 week old female C57BL/6 mice were acclimated to the vivarium for at least 4 days, weighed, and randomized into treatment groups based on body weight. 2 types of studies were conducted: acute (7 days) and chronic (28 days).

[00274] The acute DSS study is performed by adding 2.5% DSS into drinking water for 7 days. Antibodies were administered IP every 2 days (Q2D) at 10 and 30mg/kg. Mice were euthanized on day 7 with isoflurane anesthesia, exsanguination, followed by cervical dislocation. The colon were removed and analyzed for histopathology.

[00275] The chronic DSS study was performed by adding 2.0% DSS into drinking water for 1 week followed by replacing with 1 week of normal drinking water, followed by another week of 2% DSS and ending with another week of normal drinking water. Humanized antibody variants described herein were administered IV prophylactically starting on day 0 twice a week at 30 and 5 mg/kg. Mice were euthanized after 28 days with isoflurane anesthesia, exsanguination, followed by cervical dislocation. The colon was removed and analyzed for histopathology.

[00276] These results confirm that the humanized antibody variants described herein are effective for the treatment of colitis.

Example 8: Pharmacokinetics and ex vivo biodistribution of selected anti-fibrin antibodies

[00277] **Materials and Methods**

[00278] [125I]SIB-60143 and [125I]SIB-61278 Labelling Protocol

[00279] Four 125I-SIB productions were performed, employing 10 μ L (35 MBq I-125) in each case. The smaller batches were labeled to increase overall efficiency and reproducibility. Two pairs of two reactions were combined and purified by HPLC. The yield of dried 125I-SIB in each case was 25 MBq.

[00280] The pH of 60143 and 61278 stock solution (0.5 mL of each) was reduced from 8.5 to 8.0 using 2 M HEPES. The pH adjusted solutions were each then added to the dried ¹²⁵I-SIB and incubated for 1 hour at room temperature. Labelling efficiency was measured by iTLC and found to be 59% and 77% for 60143 and 61278, respectively. The reaction mixtures were then purified on NAP-5 columns, eluted with PBS.

[00281] Fractions 4-8 were combined giving 12.6 MBq of [¹²⁵I]SIB-60143 and 18.0 MBq [¹²⁵I]SIB-61278 each in 1.25 mL. The radiochemical purity was measured by iTLC and SEC-HPLC.

[00282] I-125 labelled proteins were diluted in phosphate buffered saline (PBS) to reach 1.33 mg/mL for the low dose stocks and 3.75 mg/mL for the high dose stock

[00283] Animal Model

[00284] Seventy-two female C57BL/6 mice were received from Charles River UK.

[00285] In vivo high dose pilot safety study

[00286] Two female C57BL/6 mice were injected intravenously with 30 mg/kg of 60143 and two with 30 mg/kg of 61278. The animals were monitored continuously for the first (0 to 1 h post-injection) and fourth hour post-injection (4 to 5 h post-injection). Mice were checked daily for any adverse effects at 1 and 2 days post-injection, at which point they were euthanized.

[00287] In vivo Study

[00288] For the pharmacokinetics analysis, sixty-eight female C57BL/6 mice (19.0 ± 1.3 g) were injected with 10 or 30 mg/kg of [¹²⁵I]SIB-60143 or [¹²⁵I]SIB-61278 and sacrificed at various time points (5 min, 30 min, 1 hour, 4 hours, 1 day, 3 days, 7 days, and 14 days; n=2 per time point). Blood, plasma, protein-free plasma and protein activity were counted by gamma counter. Further details regarding the study design are provided in **Table 1** below.

[00289] Thirty-two of these animals (18.6 ± 1.3 g) were also included in the biodistribution study. All mice were injected with 10 or 30 mg/kg of [¹²⁵I]SIB-60143 or [¹²⁵I]SIB-61278 and sacrificed at various time points (1 day, 3 days, 7 days, and 14 days; n=2 per time point). Further details regarding the study design are provided in **Table 2** below.

[00290] **Table 1: Study Design Summary for the PK analysis**

Time point	Samples
5 min	Blood, plasma, protein-free plasma, protein
30 min	Blood, plasma, protein-free plasma, protein
1 hour	Blood, plasma, protein-free plasma, protein
4 hours	Blood, plasma, protein-free plasma, protein
1 day	Blood, plasma, protein-free plasma, protein
3 days	Blood, plasma, protein-free plasma, protein

7 days	Blood, plasma, protein-free plasma, protein
14 days	Blood, plasma, protein-free plasma, protein

[00291] Table 2: Biodistribution Study Design Summary

Group & Route	No. Animals	Tracer	Mass Dose (mg/kg)	Radioactivity Dose (MBq/animal)	Gamma counting time point
1 IV	16	[¹²⁵ I]SIB-60143	9.8 ± 0.5	0.27 ± 0.02	24 hours 72 hours 168 hours 336 hours
2 IV	16	[¹²⁵ I]SIB-61278	9.8 ± 0.5	0.36 ± 0.02	
3 IV	16	[¹²⁵ I]SIB-60143	29.6 ± 1.9	0.27 ± 0.02	
4 IV	17	[¹²⁵ I]SIB-61278	29.3 ± 3.6	0.37 ± 0.05	

[00292] All animals from group 1 and group 2 were injected awake on day 1. Biodistribution animals (1 day, 3 days, 7 days, and 14 days) from groups 3 and 4 were also injected awake on day 1. PK-only animals (5 min, 30 min, 1 hour, 4 hour) from groups 3 and 4 were injected awake on day 2. The same production of test article formulation was used for the different injection days.

[00293] Dose Administration

[00294] Each animal was weighed on the day of dose administration. The animals ranged in weight from 16.4 to 22.5 g. Single intravenous (IV) doses were administered by using a 0.5 mL syringe to provide the appropriate dosage of 10 mg/kg for groups 1 and 2 and 30 mg/kg for groups 3 and 4. The dosing syringe was weighed before and after injection to determine amount administered to each subject.

[00295] Ex vivo Sample Preparation

[00296] Animals were sacrificed by cardiac puncture followed by exsanguination prior to organ resection. The following organs were collected for gamma counting: brain, heart, liver, kidneys, muscle, tail, stomach, large intestine, small intestine, cecum and spleen.

[00297] Analysis

[00298] Results are presented in units of percent injected dose (%ID) and percent injected dose per gram (%ID/g). The definition of these units can be found in the equations below:

[00299] The %ID for each analysed region from the *ex vivo* gamma counted data can be defined as

$$\%ID = \frac{Uptake}{Injected\ Dose} * 100 \%$$

stated in Equation 1:

[00300] Where Uptake = Radioactivity (MBq) in a particular gamma counting sample, decay-corrected to the time of injection. Injected dose= Radioactivity (MBq) injected into the subject

[00301] The %ID/g for each analysed region from the *ex vivo* gamma counted data can be defined

as stated in Equation 2:
$$\% \frac{ID}{g} = \frac{\frac{Uptake}{Injected\ Dose} * 100\%}{ROI\ weight}$$

[00302] Where, Uptake = Radioactivity (MBq) in a particular gamma counting sample, decay-corrected to the time of injection. Injected dose= Radioactivity (MBq) injected into the subject. Weight = Sample weight of the gamma counted tissue in g

[00303] Concentration values in units of $\mu\text{g/mL}$ can be defined for the *ex vivo* gamma counting data according to Equation 3:
$$\frac{\mu\text{g}}{\text{mL}} = \frac{\%ID}{g} \times \frac{Injected\ Dose\ (\mu\text{g})}{100\ \%ID} / \frac{1\ \text{mL}}{1\ \text{g}}$$

[00304] Where, Injected Dose = Antibody mass (μg) injected into the subject. Assumption: tissue density of 1 g/mL.

[00305] Gamma Counting Analysis for Biodistribution

[00306] The activity of each collected tissue was measured in units of counts per minute (CPM). Triplicate aliquots of the radiotracer were also assayed in the gamma counter in order to calculate a factor for converting counts to mass of injected material (g/CPM). Values were corrected for background radiation and converted to percent injected dose (%ID) and percent injected dose per gram (%ID/g).

[00307] Gamma Counting Analysis for PK Study

[00308] The activity of each collected tissue was measured in units of counts per minute (CPM). Triplicate aliquots of the radiotracer were also assayed in the gamma counter in order to calculate a factor for converting counts to mass of injected material (g/CPM). Values were then corrected for background radiation and converted to percent injected dose (%ID) and percent injected dose per gram (%ID/g).

[00309] For the PK analysis, concentration (%ID/g) of radiotracer in blood from blood subsample gamma counting was pooled from 2 mice and calculated as follows:

$$\text{Mass (injectate in sample) [g]} = \text{CPM(sample)} \times \frac{\text{Mass (injectate in standard) [g]}}{\text{CPM(standard)}}$$

$$\text{Injected Mass (pooled) [g]} = \frac{\text{Mass (injectate in Mouse 1) [g]} + \text{Mass (injectate in Mouse 2) [g]}}{2}$$

$$\%ID\ (\text{sample}) = \frac{\text{Mass (injectate in sample) [g]}}{\text{Injected Mass (pooled) [g]}} \times 100$$

$$\%ID/\text{mL (sample)} = \frac{\%ID\ (\text{sample})}{\text{Volume (sample) [mL]}}$$

[00310] Subsampled blood and plasma %ID values were also extrapolated to total (whole body) blood and plasma values, respectively. For extrapolation, the ratio of blood volume/body weight = 0.072 mL/kg was used (Diehl et al., 2001). For calculating whole plasma, a haematocrit value of 0.387 was used.

[00311] Non-compartmental analysis

[00312] %ID/mL values were converted to units of µg/mL prior to non-compartmental analysis using the following equation:

$$\text{Concentration } (\mu\text{g/mL}) = \frac{\text{Mass (injectate in sample)} [g]}{\text{Volume (sample)} [mL]} \times \frac{1 \times 10^6 [\mu\text{g}]}{1 [g]}$$

[00313] The regression was performed on µg/mL values with Python using Phoenix WinNonlin (Certara) rules to determine the terminal clearance rate λ_z . PK parameters were calculated as follows:

$$\text{AUC} \quad AUC [\mu\text{g} \cdot \text{h} \cdot \text{mL}^{-1}] = \int_0^{tn} C(t) dt$$

$$\text{AUC (0 - 24)} \quad AUC [\mu\text{g} \cdot \text{h} \cdot \text{mL}^{-1}] = \int_0^{24} C(t) dt$$

$$\text{AUC (0 - } \infty \text{) (AUC}_{inf}\text{)} \quad AUC [\mu\text{g} \cdot \text{h} \cdot \text{mL}^{-1}] = \int_0^{tn} C(t) dt + \frac{C(tn)}{\lambda_z}$$

$$\text{AUC}_{Tail} \quad \frac{AUC_{mf} - AUC}{AUC_{mf}} \times 100$$

$$\text{Volume of Distribution} \quad V_D [mL] = \frac{\text{Dose } [\mu\text{g}]}{AUC_{mf} [\mu\text{g} \cdot \text{h} \cdot \text{mL}^{-1}] \times \lambda_z}$$

$$\text{Clearance} \quad CL [mL \cdot \text{h}^{-1}] = \frac{\text{Dose } [\mu\text{g}]}{AUC_{mf} [\mu\text{g} \cdot \text{h} \cdot \text{mL}^{-1}]}$$

[00314] **Results**

[00315] PK analysis

[00316] A range of PK parameters was calculated for the radiolabeled antibodies [125I]SIB-60143 and [125I]SIB-61278 at 10 mg/kg and 30 mg/kg (Figure 15A, figure 15B, and Table 3). There was no indication of instability in vivo with >95% of activity protein-bound (Figure 15A and 15B). About 50-70% of test article was removed from the blood and plasma after 24 hours post-injection for both antibodies at both dose levels. The elimination half-life of [125I]SIB-60143 in the blood and plasma at both doses was in the 275-375 hours range. The elimination half-life of [125I]SIB-61278 was longer than other antibodies at both dose levels; 550-600 hours in plasma and 775-825 hours in blood. The clearance values were similar when comparing the two dose levels for each antibody in blood and plasma independently.

[00317] Table 3: NCA analysis results of [¹²⁵I]SIB-60143 and [¹²⁵I]SIB-61278 at 10 mg/kg and 30 mg/kg

	Regression range	[¹²⁵ I]SIB-60143 (10 mg/kg)		[¹²⁵ I]SIB-60143 (30 mg/kg)		[¹²⁵ I]SIB-61278 (10 mg/kg)		[¹²⁵ I]SIB-61278 (30 mg/kg)	
		Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma
C_{max} (mg/mL)	N/A	109	205	270	500	96	191	314	585
t_{1/2α} (h)	5 min to 4 h	7.7	6.8	6.2	6.0	7.6	6.5	5.3	4.1
t_{1/2} (h)	24 h to 14 d	291	316	350	309	820	557	789	597
λ_z (h⁻¹)	24 h to 14 d	0.0024	0.0022	0.0020	0.0022	0.0008	0.0012	0.0009	0.0012
t_{1/2} (h)	3 d to 14 d	281	325	398	371	876	503	732	398
λ_z (h⁻¹)	3 d to 14 d	0.0025	0.0021	0.0017	0.0019	0.0008	0.0014	0.0009	0.0017
Vd (mL)	24 h to 14 d	3.64	2.11	4.27	2.36	3.80	2.02	4.30	2.32
CL (mL/h)	24 h to 14 d	0.0087	0.0046	0.0084	0.0053	0.0032	0.0025	0.0038	0.0027
AUC (mg/mL.h)	5 min to 14 d	12000	21000	32000	56000	14000	25000	39000	69000
AUC_∞ (mg/mL.h)	3 d to 14 d	22000	40000	66000	105000	56000	72000	149000	210000

[00318] Biodistribution

[00319] *Ex vivo* biodistribution of both antibodies was determined at 24, 72, 168 and 336 hours post-injection. Figure 16A shows [¹²⁵I]SIB-60143 at 10 mg/kg in mice over time. Figure 16B shows [¹²⁵I]SIB-60143 at 30 mg/kg in mice over time. Figure 16C shows [¹²⁵I]SIB-61278 at 10 mg/kg in mice over time. Figure 16D shows [¹²⁵I]SIB-61278 at 30 mg/kg in mice over time. The pattern of distribution was similar for both antibodies at both doses, with low brain concentration (between $0.39 \pm <0.01$ and 0.91 ± 0.51 %ID/g), and uptake in heart (between 3.50 ± 0.03 and 10.69 ± 2.02 %ID/g), kidneys (between 3.28 ± 0.01 and 8.40 ± 1.37 %ID/g), liver (between 1.85 ± 0.01 and 5.12 ± 0.85 %ID/g) and spleen (between 1.77 ± 0.05 and 5.27 ± 0.55 %ID/g). No difference of concentration was observed with increasing dose. The uptake of 61278 at 14 days was in higher in all organs than 60143, consistent with a longer elimination half-life.

[00320] 50-70% of test article was removed from the blood and plasma after 24 hours post-injection for both antibodies at both dose levels. The elimination half-life of [¹²⁵I]SIB-60143 in blood and plasma at all dose ranges was in the 275-375 hours range. The elimination half-life of [¹²⁵I]SIB-61278 was longer than other antibodies at both dose levels; 550-600 hours in plasma and 775-825 hours in blood. The biodistribution data was comparable between both antibodies at both dose levels. The uptake of [¹²⁵I]SIB-61278 at 14 days was higher in all organs than [¹²⁵I]SIB-60143, consistent with a longer elimination half-life.

Example 9: Crystal structure of the Fab of Antibody Clone 60143

[00321] The X-ray crystal structure of the Fab of antibody clone ABI-60143, comprising a heavy chain and light chain variable domain, in complex with fibrinogen gamma peptide P2 was solved at 1.5 Å resolution. The crystal described was grown using the hanging drop method of vapour diffusion in a 96 well plate with a precipitant solution containing 0.1 M sodium cacodylate pH 5.5 and 25% PEG 4000. The crystal was cryo-cooled without additional cryo-protectant by capturing it in a loop directly from the growth drop and plunging it into liquid nitrogen. A data set was collected at the Swiss Light Source (SLS), beamline X06DA (PXIII).

[00322] Data processing in MOSFLM (Battye *et al.*, 2011) (CCP4) and AIMLESS (Evans & Murshudov, 2013) (CCP4) indicated that the most likely space group was *P212121* with unit cell dimensions $a = 67.9 \text{ Å}$, $b = 73.3 \text{ Å}$, $c = 93.6 \text{ Å}$ and $\alpha = \beta = \gamma = 90.0^\circ$, giving a total cell volume of 465741.4 Å^3 . Calculation of the Matthews coefficient ($2.3 \text{ Å}^3/\text{Da}$ and 46.6% solvent content) indicated that there was most probably one complete Fab-ABI-60143-P2 complex per asymmetric unit. Models for use in molecular replacement (MR) were chosen by BLAST searching the sequences of the Fab heavy and light chains against the PDB. Models with highest sequence identity were 6ani (Fab heavy chain) and 3pp3 (Fab light chain). The large number of Fab crystal structures in the PDB has revealed a large variety in the elbow angles present between variable and constant domains. This variety in elbow angles can cause the overall tertiary structure of two otherwise highly homologous Fab fragments to be significantly different, which in turn causes MR to fail. For this reason, the hinge regions between the variable and constant domains of the heavy and light chains were removed. Four separate MR search ensembles were generated (VH, CH, VL and CL domains). Amino acid residues were trimmed from the CDRs of the heavy and light variable domain models after visual inspection in COOT to prevent any potential clashes in the interface with P2 that might also cause MR to fail. All four of the input search ensembles that were required to build a complete Fab were correctly located by MR using PHASER (McCoy *et al.*, 2007) (CCP4). The MR output model was given 30 cycles of jelly body refinement using REFMAC5 (Vagin *et al.*, 2004) (CCP4). The protein sequence was mutated to match that of Fab using CHAINSAW (Stein, 2008) (CCP4). The Fab ABI-60143 model was improved iteratively through successive cycles of model building and refinement until all of the ordered regions of protein visible in the electron density maps were complete. The P2 peptide chain was added to the model by hand in COOT and the complete complex model was refined in REFMAC5. The final protein model contained residues 410-421 from chain A (peptide P2), 1-127 and 134-214 from chain H (Fab heavy chain) and 1-213 from chain L (Fab light chain). Final Rwork = 16.8%, Rfree = 20.5%.

[00323] There was one copy each of Fab ADI-60143 and peptide P2 per asymmetric unit. The Fab ADI-60143 CDR canonical structures were analyzed in accordance with the PyIgClassify database (Adolf-Bryfogle *et al.*, 2014). The heavy chain CDRs were classified as follows: H1-13-1 (CDR-length-cluster) and H2-10-1. CDR H3 was not classified. The light chain CDRs were classified as follows: L1-16-1, L2-8-1 and L3-9-cys7-1.

[00324] Each P2 peptide bound to a single Fab. The fold was similar, but not the same as that seen in published fibrinogen gamma chain crystal structures such as PDB ID: 1fzc.

Table: 4 Fab ADI-60143 and peptide P2 interface analysis

List of interface hydrogen bonds Monomer 1	Length (Å)	Monomer 2
A:LYS 411 [NZ]	2.83	H:ASP 54 [OD2]
A:LYS 411 [NZ]	2.78	H:ASP 52 [OD2]
A:LYS 411 [NZ]	3.34	H:ASP 54 [OD1]
A:ASN 416 [O]	3.95	H:SER 95 [OG]
A:ASN 416 [O]	3.42	H:LYS 96 [N]
A:ASN 416 [O]	3.46	H:LYS 96 [O]
A:ARG 417 [NE]	3.43	H:TRP 33 [NE1]
A:ARG 417 [NE]	3.71	H:SER 31 [O]
A:ARG 417 [NH1]	3.50	H:SER 31 [O]
A:ARG 417 [O]	3.68	H:SER 95 [OG]
A:ARG 417 [O]	2.83	H:HIS 35 [NE2]
A:LEU 418 [O]	3.28	L:ASN 91 [OD1]
A:THR 419 [O]	2.94	H:LYS 96 [N]
A:ILE 420 [N]	3.58	L:TYR 36 [OH]
A:ILE 420 [O]	2.52	L:TYR 36 [OH]
A:GLY 421 [N]	3.02	H:SER 94 [O]
A:GLY 421 [OXT]	3.77	H:GLY 102 [N]
A:GLY 421 [OXT]	3.74	H:GLY 101 [O]

Table: 5 Fab ADI-60143 Participating Interface residues

Peptide P2	Fab ADI-60143
A:LYS 411	H:SER 31
A:ILE 412	H:TRP 33
A:ILE 413	H:HIS 35
A:PHE 415	H:LEU 50
A:ASN 416	H:ASP 52
A:ARG 417	H:ASP 54
A:LEU 418	H:TYR 56
A:THR 419	H:ALA 93
A: ILE 420	H:SER 94
A: GLY 421	H:LYS 96
	H:PRO 97
	H:GLY 101
	H:GLY 102
	H:TRP 103
	L:HIS 27
	L:TYR 32
	L:TYR 36
	L:LEU 46
	L:ASN 91
	L:LEU 92

L:LEU 94
L:LEU 96

Table 6: Data collection, processing and refinement statistics

Synchrotron, Beam line	SLS, PXIII
Date of data collection	26/08/2021
Wavelength (Å)	1.286281
Detector type	DECTRIS PILATUS 2M-F
Transmission (%)	100
Temperature (K)	100
Exposure time (s)	0.05
Oscillation range per frame (°)	0.10
Overall rotation (°)	180
Resolution range (Å) (overall and last shell)	46.81 – 1.50 (1.53 – 1.50)
Number of observed reflections (overall and last shell)	462407 (14052)
Number of unique reflections (overall and last shell)	75227 (3612)
Multiplicity (overall and last shell)	6.1 (3.9)
Completeness (%) (overall and last shell)	99.7 (97.7)
R _{merge} (%) (overall and last shell)	9.2 (104.7)
Mean I/sigma (overall and last shell)	11.2 (1.1)
CC(1/2) (overall and last shell)	0.998 (0.429)
Space group	<i>P212121</i>
Unit cell parameters (Å), (°)	67.89 73.28 93.62 90.00 90.00 90.00

Refinement program	REFMAC5
Resolution range (Å)	46.81 – 1.50
Number of reflections (working/test)	71309 / 3845
R _{work} (%)	16.8
R _{free} (%)	20.5
Protein residues modeled	418
Number of protein atoms modeled	3320
Number of water atoms modeled	721
RMSD Bond lengths (Å)	0.012
RMSD Bond angles (°)	1.690
Mean protein B value (Å ²)	16.4
Mean water B value (Å ²)	29.1
Ramachandran plot favored (%)	97.85
Ramachandran plot allowed (%)	1.67
Ramachandran plot outlier region (%)	0.48

Example 10: Crystal structure of the Fab of Antibody Clone ADI-61278

[00325] The X-ray crystal structure of Fab antibody clone ADI61278, comprising a heavy chain and light chain variable domain, in complex with fibrinogen gamma peptide P2 was solved at 1.8 Å resolution. The crystal described was grown using the hanging drop method of vapour diffusion in a

96 well plate with a precipitant solution containing 1% (w/v) Tryptone, 0.001 M sodium azide, 0.05 M sodium HEPES pH 7.0 and 20% PEG 3350. The crystal was cryo-cooled by brief transfer into a solution containing four parts precipitant solution and one part 100% (v/v) glycerol, before capturing it in a loop and plunging it into liquid nitrogen. A data set was collected at the Diamond Light Source (DLS), beamline i03.

[00326] Data processing in MOSFLM (Battye et al., 2011) (CCP4) and AIMLESS (Evans & Murshudov, 2013) (CCP4) indicated that the most likely space group was P2₁2₁2₁ with unit cell dimensions $a = 47.0 \text{ \AA}$, $b = 79.0 \text{ \AA}$, $c = 144.3 \text{ \AA}$ and $\alpha = \beta = \gamma = 90.0^\circ$, giving a total cell volume of 534840.2 $\text{\AA}^3$. Calculation of the Matthews coefficient (2.8 $\text{\AA}^3/\text{Da}$ and 55.8% solvent content) indicated that there was most probably one complete Fab- ADI61278 -P2 complex per asymmetric unit. The Fab- ADI61278 model was chosen for use in molecular replacement (MR). The large number of Fab crystal structures in the PDB has revealed a large variety in the elbow angles present between variable and constant domains. This variety in elbow angles can cause the overall tertiary structure of two otherwise highly homologous Fab fragments to be significantly different, which in turn causes MR to fail. For this reason, the hinge regions between the variable and constant domains of the heavy and light chains were removed. Two separate MR search ensembles were generated (VH-VL heterodimer and CH-CL heterodimer). Both of the input search ensembles that were required to build a complete Fab were correctly located by MR using PHASER (McCoy et al., 2007) (CCP4). The MR output model was given 30 cycles of jelly body refinement using REFMAC5 (Vagin et al., 2004) (CCP4). The protein sequence was mutated to match that of Fab- ADI61278 using CHAINSAW (Stein, 2008) (CCP4). The Fab ADI61278 model was improved iteratively through successive cycles of model building and refinement until all of the ordered regions of protein visible in the electron density maps were complete. The peptide P2 chain was added to the model by hand in COOT and the complete complex model was refined in REFMAC5. The final protein model contained residues 410-421 from chain A (peptide P2), 1-126 and 133-214 from chain H (Fab heavy chain) and 1-213 from chain L (Fab light chain). Final Rwork = 19.1%, Rfree = 24.0%.

[00327] There was one copy each of Fab ADI61278 and peptide P2 per asymmetric unit. The Fab ADI61278 CDR canonical structures were analysed in accordance with the PyIgClassify database (Adolf-Bryfogle et al., 2014). The heavy chain CDRs were classified as follows: H1-13-1 (CDR-length-cluster), H2-10-1 and H3-8-1. The light chain CDRs were classified as follows: L1-16-1, L2-8-1 and L3-9-cys7-1. Each P2 peptide bound to a single Fab. The fold is similar to, but not the same as that seen in published fibrinogen gamma chain crystal structures such as PDB ID: 1fzc.

Table 7: Fab ADI-61278 and peptide P2 interface analysis

Monomer 1	Length (Å)	Monomer 2
A:LYS 411 [NZ]	2.71	H:ASP 54 [OD2]
A:LYS 411 [NZ]	2.74	H:ASP 52 [OD2]
A:LYS 411 [NZ]	3.34	H:ASP 54 [OD1]
A:ASN 416 [O]	3.31	H:ASP 96 [N]
A:ASN 416 [O]	3.65	H:ASP 96 [OD1]
A:ASN 416 [O]	3.62	H:ASP 96 [OD2]
A:ASN 416 [OD1]	3.22	L:GLN 50 [NE2]
A:ARG 417 [NE]	3.25	H:TRP 33 [NE1]
A:ARG 417 [NE]	4.00	H:ASP 96 [OD1]
A:ARG 417 [NH1]	3.75	H:TRP 33 [NE1]
A:ARG 417 [NH1]	3.32	H:SER 31 [O]
A:ARG 417 [NH2]	3.08	H:SER 31 [O]
A:ARG 417 [NH2]	3.87	H:SER 95 [OG]
A:ARG 417 [NH2]	2.90	H:ASP 96 [OD1]
A:ARG 417 [NH2]	3.71	H:ASP 96 [OD2]
A:ARG 417 [O]	2.78	H:HIS 35 [NE2]
A:THR 419 [O]	3.13	H:ASP 96 [N]
A:THR 419 [O]	3.83	H:HIS 35 [NE2]
A:ILE 420 [N]	3.48	L:TYR 36 [OH]
A:ILE 420 [O]	2.57	L:TYR 36 [OH]
A:GLY 421 [N]	2.71	H:SER 94 [O]
A:GLY 421 [O]	3.64	H:THR 98 [N]
A:GLY 421 [O]	2.94	H:GLY 101 [N]
A:GLY 421 [OXT]	3.96	H:ASP 96 [N]
A:GLY 421 [OXT]	3.62	H:SER 94 [O]
A:GLY 421 [OXT]	3.58	H:SER 95 [O]
A:GLY 421 [OXT]	3.00	H:THR 98 [N]
A:GLY 421 [OXT]	3.89	H:THR 98 [OG1]
A:GLY 421 [OXT]	3.63	H:GLY 101 [N]
A:GLY 421 [OXT]	3.02	H:ALA 97 [N]

Table 8: List of participating interface residues

Peptide P2	Fab ADI-61278
A:LYS 411	H:SER 31
A:ILE 413	H:TYR 32
A:PHE 415	H:TRP 33
A:ASN 416	H:HIS 35
A:ARG 417	H:TRP 47
A:LEU 418	H:ASP 52
A:THR 419	H:ASP 54
A: ILE 420	H:TYR 56
A: GLY 421	H:SER 94
	H:SER 95
	H:ASP 96
	H:ALA 97
	H:THR 98
	H:GLY 101
	H:GLY 102
	H:TRP 103
	L:HIS 27
	L:TYR 32
	L:TYR 36
	L:LEU 46
	L:TYR 49
	L:GLN 50
	L:ALA 91
	L:LEU 92
	L:LEU 94

L:LEU 96

Table 9: Data collection, processing statistics and refinement statistics

Synchrotron, Beam line	DLS, i03
Date of data collection	24/09/2021
Wavelength (Å)	0.9763
Detector type	DECTRIS EIGER2 XE 16M
Transmission (%)	23.84
Temperature (K)	100
Exposure time (s)	0.004
Oscillation range per frame (°)	0.10
Overall rotation (°)	360
Resolution range (Å) (overall and last shell)	44.65 – 1.80 (1.84 – 1.80)
Number of observed reflections (overall and last shell)	681993 (41185)
Number of unique reflections (overall and last shell)	50679 (2967)
Multiplicity (overall and last shell)	13.5 (13.9)
Completeness (%) (overall and last shell)	100.0 (100.0)
R _{merge} (%) (overall and last shell)	9.5 (175.5)
Mean I/sigma (overall and last shell)	14.7 (1.4)
CC(1/2) (overall and last shell)	0.999 (0.669)
Space group	P2 ₁ 2 ₁ 2 ₁
Unit cell parameters (Å), (°)	46.95 78.96 144.26 90.00 90.00 90.00
Refinement program	REFMAC5
Resolution range (Å)	44.65 – 1.80
Number of reflections (working/test)	48037 / 2583
R _{work} (%)	19.1
R _{free} (%)	24.0
Protein residues modeled	419
Number of protein atoms modeled	3310
Number of water atoms modeled	421
RMSD Bond lengths (Å)	0.005
RMSD Bond angles (°)	1.300
Mean protein B value (Å ²)	32.9
Mean water B value (Å ²)	42.3
Ramachandran plot favored (%)	97.61
Ramachandran plot allowed (%)	2.15
Ramachandran plot outlier region (%)	0.24

Example 11: ADI-60143 and ADI-61278-Fabs both bind at the C-terminus of P2-Peptide and show most differences in the CDR-3 Regions

[00328] The crystal structures of the FABs of antibody clones ADI-60143 and ADI-61278 described above were super-imposed and the P2 peptide binding sites were compared as shown in Figures 17 and 18. These results show that ADI-60143 and ADI-61278-Fabs both bind at the C-terminus of P2-Peptide and also show most differences are located in the CDR-3 Regions of the two Fabs.

[00329] The binding of the ADI-60143 and ADI-61278 Fabs to P2 peptide was determined as described in Example 2 using Octet RED384 (Figure 19). Amino acid variations in CDR1

and CDR3 explain differences in binding on- and off-rates between ADI-60143 and ADI-61278-Fabs interacting with P2-peptide.

[00330] Binding of ADI-60143 Fab and full length ADI-60143 IgG to rat, mouse or human P2 peptide and extended P2 peptide was also determined by ELISA (Figures 20 and 21). Similar binding profiles were observed for the three P2 peptides from the different species. However, the extended P2 peptide of the three species, did not bind well to ADI-60143 IgG (Figure 21).

Example 12: Therapeutic Treatment with ADI-60143 Inhibits Microglia Activation and Macrophage Recruitment in Fibrin-Induced Encephalitis (FIE) PD Model

[00331] In order to test the efficacy of the affinity matured antibody clones for inhibition of microglia activation and macrophage recruitment in treatment of neural degenerative disease and inflammation, a mouse model of fibrin-induced encephalitis (FIE) was used. Six mice per group, for a total of 78 mice, were administered fibrinogen by stereotaxic injection into the corpus callosum. Antibodies were administered by intravenous (I.V.) injection. Four hrs after fibrinogen injection, mice were given an I.V. injection of the affinity matured anti-fibrin humanized antibodies (10 mg/kg or 30 mg/kg). Brain tissue was prepared at three days post-injection. 73 mice samples were included for immunohistochemistry and quantification. Coronal sections (30 um) were prepared on the Cryostat. Sections were incubated with anti-Iba-1 antibody (Microglia marker, 1:750) to detect microglial activation and anti-Mac-2 antibody (Macrophage infiltration marker, 1:750). Immunoreactivity of Iba-1 (Iba-1+ area) and Mac-2 (Mac-2+ area) was then calculated, and image collection and quantification was performed in a blinded manner.

[00332] As shown in Figure 22, there was a significant reduction in both microglia activation and macrophage recruitment in mice injected with 30 mg/kg ADI-60143. The reduction was also greater than what was measured in mice injected with the parental humanized 5B8 antibody (TIIN227), that had not undergone affinity maturation. These results confirm that the affinity matured antibody clone 60143 is therapeutically efficacious for the inhibition of microglia activation and macrophage recruitment for treatment of neural degenerative disease or conditions and/or neural inflammation.

Example 13: Antibody clone ADI-60143 is Efficacious in a Preclinical Model of Multiple Sclerosis

[00333] In order to test the therapeutic efficacy of the affinity matured antibody clones for treatment of multiple sclerosis (MS), a pre-clinical mouse model of MS, experimental autoimmune encephalomyelitis (EAE) was used. EAE was induced by immunization of PLP₁₃₉₋₁₅₁/CFA (Hooke Kit™ PLP₁₃₉₋₁₅₁/ CPA Emulsion, catalog number EK-0120, Hooke Laboratories, Lawrence MA) on day zero. EAE mice were therapeutically injected starting on day 2 and lasting through day 44 for dexamethasone and through day 33 for all other groups, with PBS alone, isotype control- human IgG1 (huIgG) alone, antibody clone 60143 (ABI-60143) or dexamethasone by intraperitoneal injection at 5 mg/kg, two times per week. Spinal cord tissue from the mice was harvested from mice with EAE at peak disease or healthy mice, and immunohistochemical (IHC) staining of the spinal cord tissue was performed to determine antibody drug distribution to the spinal tissue and demyelination.

[00334] For the IHC staining, freshly harvested, non-fixed tissue was placed in OCT compound inside a cryomold. The cryomold was placed in isopentane mixed with dry ice for freezing, and the frozen tissue kept at -80 °C. Tissue sections were cut 10 µm thick in a cryostat and mounted on slides. Slides were stained by fixing immediately in ice-cold 4% para-formaldehyde in PBS for 10 minutes at 4 °C. Slides were blocked to prevent non-specific binding of primary antibodies to the tissue by incubating in blocking buffer (3% bovine serum albumin in PBS; Millipore Sigma, A9576) for 30 minutes at 25 °C. To detect biotinylated antibody injected in tissue prior to sectioning, Cy3-conjugated streptavidin (1:100; SA1010, Thermo Fischer Scientific) was diluted in PBS, applied to tissue sections, and incubated for 30 minutes at 25 °C. For fibrin staining, antibody (1:2000, rabbit polyclonal anti-fibrinogen) diluted in PBS was added to tissue sections and incubated for 60 minutes at 25 °C. FITC donkey anti-rabbit IgG (1:500 in PBS, Jackson ImmunoResearch) was then added to each section, and incubated for 30 minutes at 25 °C.

[00335] As shown in Figure 24, the affinity matured antibody (ABI-60143), was localized to the spinal cord in EAE mice at peak disease. This confirms that the affinity matured antibodies are well distributed to the diseased spinal tissue.

[00336] Percent demyelination of tissue sections was quantified by determination of the percent area lacking staining of myelin basic protein (MBP). As shown in Figure 24A, the percent demyelination was significantly reduced in a dose dependent manner in mice administered antibody clone 60143.

[00337] The mice were also assessed for hind limb paralysis and clinical score. As shown in Figure 24B, there was dose-dependent decrease in demyelination and complete hind limb paralysis in EAE mice administered the affinity matured antibody clone 60143.

[00338] EAE Clinical score was assessed by the criteria as shown in the Table below:

Score	Clinical Observations
0	No obvious changes in motor functions of the mouse in comparison to non-immunized mice. When picked up by the tail, the tail has tension and is erect. Hind legs are usually spread apart. When the mouse is walking, there is no gait or head tilting.
1	Limp tail. When the mouse is picked up by the tail, instead of being erect, the whole tail drapes over your finger.
2	Limp tail and weakness of hind legs. When mouse is picked up by tail, legs are not spread apart, but held closer together. When the mouse is observed when walking, it has aberrant wobbly walk.
3	Limp tail and complete paralysis of hind legs (most common). OR Limp tail with paralysis of one front and one hind leg. OR ALL of: • Severe head tilting, • Walking only along the edges of the cage, • Pushing against the cage wall, • Spinning when picked up by the tail.
4	Limp tail, complete hind leg and partial front leg paralysis. Mouse is minimally moving around the cage but appears alert and feeding. Usually, euthanasia is recommended after the mouse scores level 4 for 2 days. When the mouse is euthanized because of severe paralysis, score of 5 is entered for that mouse for the rest of the experiment.
5	Complete hind and complete front leg paralysis, no movement around the cage. OR Mouse is spontaneously rolling in the cage. OR Mouse is found dead due to paralysis.

[00339] Both negative control groups (Vehicle and Isotype control) developed EAE as expected for this model. Mean maximum severity (MMS) of the first wave of EAE was 2.4 and 2.5 for the Vehicle and the Isotype control group, respectively. The incidence of relapses was 73% and 60% for the Vehicle and the Isotype control group, respectively. MMS of the relapse period was 2.3 and 1.9 for the Vehicle and the Isotype control group, respectively.

Disease in these groups had typical course and severity for this model. As shown in Figure 25, mice administered ABI-60143-LALA IgG (antibody clone 60143 comprising Fc stabilization LALA mutations) developed reduced disease, as demonstrated by a significantly reduced mean EAE clinical score, with no detectable disease at 17 days after immunization.

[00340] In order to confirm that the affinity matured antibodies reduced inflammation, segments from cervical, thoracic, and lumbar regions of spinal cord (3 segments) were prepared and stained with: H and E, and anti-CD4/anti-CD11b (dual-label) antibodies. Inflammatory foci of approximately 20 cells were counted in each H&E-stained section. When inflammatory infiltrates consisted of more than 20 cells, an estimate was made of how many foci of 20 cells were present. As shown in Figure 26A, there was a significant reduction in the number of inflammatory foci in tissue sections from EAE mice administered antibody clone ABI-60143 IgG or ABI-60143-LALA IgG compared to isotype control. There was also a significant reduction in pro-inflammatory marker CD11b in tissue sections from EAE mice administered antibody clone ABI-60143 IgG or ABI-60143-LALA IgG compared to isotype control (Figure 26B). These results confirm that the affinity matured antibodies ABI-60143 IgG and ABI-60143-LALA IgG are capable of reducing inflammation in a pre-clinical model of Multiple Sclerosis.

[00341] Taken together, these results confirm that the affinity matured humanized anti-fibrin antibody is therapeutically efficacious in a pre-clinical model of Multiple Sclerosis.

Example 14: Anti-Fibrin P2 Treatment Decreases Inflammation in Uveitis Model

[00342] Experimental autoimmune uveitis (EAU) is an organ specific autoimmune disease that targets the neural retina. This autoimmune response is induced when animals are immunized with retinal antigens (Interphotoreceptor Retinoid-Binding Protein [IRBP], in this case). In order to confirm the therapeutic role of anti-fibrin treatment in inflammatory eye conditions or diseases, the efficacy of the anti-fibrin affinity matured antibodies were tested in a rat experimental autoimmune uveitis (EAU) model after intravitreal administration of the anti-fibrin antibodies.

[00237] In this study, 52 Lewis rats were divided into six groups namely PBS (Group 1), Isotype control (Group 2), ABI-60143 low dose (Group 3), ABI-60143 high dose (Group 4), FTY-720 positive control (Group 5), and Naïve (Group 6). Animals from all groups, except Group 6, were immunized with an emulsion of IRBP in Complete Freund's Adjuvant (CFA) on Day 0. Similarly, animals from Group 1-4 received a single intravitreal injection of sponsors test article once on Day 0. Animals in Group 5 received once daily oral

administration of positive control FTY-720. After a period of 8-10 days, immunized animals developed uveitis in each eye. Clinical evaluations were performed for all the animals at baseline, day 4, 7, 11, and 14 to follow the extent of diseases developed. Clinical observations were performed as follows:

Frequency: Once on each study day

Procedure: Groups were randomized ahead of evaluations to keep the examiner masked. Animals were observed under a dissection microscope and scored on a scale of 0-4 based on their anterior clinical disease. Photographs of the anterior chamber were taken at the time of clinical evaluations.

Clinical observation scoring:

- 0-0.5: No disease; eye is translucent. Some blood vessels in the iris may be dilated.
- 1: Engorged blood vessels in iris; abnormal pupil contraction (or dilation).
- 2: Slight haziness to the anterior chamber.
- 3: Moderately opaque anterior chamber, but pupil still visible.
- 4: Opaque anterior chamber and obscured pupil.

[00238] All animals were euthanized on day 14 and immediately following euthanasia, whole eyes (OU) were collected, Upon verification of death, both eyes of each animal were carefully removed. One eye was collected for histological analysis, and the other eye was collected for cytokine analysis. Eyes for cytokine analysis were hemisected and retina was collected. Each eye was carefully orientated for optimal microscopic examination prior to wax embedding. Sections (5µm) were cut and stained with hematoxylin and eosin for histological examination and scoring according to the following scale summarized below and as described by Caspi, et al. (2012). Histological analysis was masked to the examiner.

Clinical Scoring/Uveitis grading was determined as follows:

- 0: No disease, normal retinal architecture.
- 0.5: Trace. <1/4 Mild inflammatory cell infiltration of the retina with or without photoreceptor damage.
- 1: $\geq 1/4$ Mild inflammation and/or photoreceptor outer segment damage.

2: $\geq \frac{1}{4}$ Mild to moderate inflammation and/or lesion extending to the outer nuclear layer.

3: $\geq \frac{1}{4}$ Moderate to marked inflammation and or lesion extending to the inner nuclear layer.

4: $\geq \frac{1}{4}$ Severe inflammation and/or full-thickness retinal damage.

[00343] As shown in Figure 27, rats administered a low or high dose of the murinized ADI-60143 – LALA Fc stabilized antibody clone exhibited a significantly reduced clinical uveitis score on day 14 of the study. These results confirm that the affinity matured anti-fibrin antibodies decreased inflammation in subjects with uveitis and are therapeutically effective in a pre-clinical model of eye conditions related to vascular defects of the eye, such as uveitis.

[00344] While the invention has been particularly shown and described with reference to a preferred embodiment and various alternate embodiments, it will be understood by persons skilled in the relevant art that various changes in form and details can be made therein without departing from the spirit and scope of the invention.

[00345] All references, issued patents and patent applications cited within the body of the instant specification are hereby incorporated by reference in their entirety, for all purposes.

INFORMAL SEQUENCE LISTING

Description	Sequence	SEQ ID NO
56666 CDR-H1	YTFTSYWIH	SEQ ID NO: 1
56666 CDR-H2	LIDPSDSYTNYNQKFRG	SEQ ID NO: 2
56666 CDR-H3	ASSDPTGG	SEQ ID NO: 3
56666 CDR-L1	RSSKSLLISSGITYLS	SEQ ID NO: 4
56666 CDR-L2	QMSNLAS	SEQ ID NO: 5
56666 CDR-L3	AQNLELPLT	SEQ ID NO: 6
56666 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWIHWVRQAPGQGLE WMGLIDPSDSYTNYNQKFRGRVTMTVD TSTSTAYMELSSLRSEDTAVY YCASSDPTGGWGQGTTVTVSS	SEQ ID NO: 7
56666 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVI HQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 8
56666 CL	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDYSLSSLTLSKADYEEKHKVYACEVTHQGLSSP VTKSFNRGEC	SEQ ID NO: 9
56666 VL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLAGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLELP LTFGGGTKEIK	SEQ ID NO: 10
56666 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWIHWVRQAPGQGLE WMGLIDPSDSYTNYNQKFRGRVTMTVD TSTSTAYMELSSLRSEDTAVY YCASSDPTGGWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG	SEQ ID NO: 11
56666 VL+CL	AEDVGVYYCAQNLELPLTFGGGTKEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDYSLSSLTLSKADYEEKHKVYACEVTHQGLSSP VTKSFNRGEC	SEQ ID NO: 12
61289 CDR-H1	YTFTSSWIH	SEQ ID NO: 13
61289 CDR-H2	LIDPSDSYTNYNQKFRG	SEQ ID NO: 14
61289 CDR-H3	ASSDPHGG	SEQ ID NO: 15
61289 CDR-L1	RSSKSLHSSGITMLS	SEQ ID NO: 16
61289 CDR-L2	QMSNLAS	SEQ ID

		NO: 17
61289 CDR-L3	AQSLELPLT	SEQ ID NO: 18
61289 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSSWIHWVRQAPGQGLEW MGLIDPSDSYTNYNQKFRGRVTMTVD TSTSTAYMELSSLRSEDTAVYY CASSDPHGGWGQGTTTVTVSS	SEQ ID NO: 19
61289 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 20
61289 CL	RTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	SEQ ID NO: 21
61289 VL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITMLS WYLQKPGQSPQL LIYQMSNLASGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQSLELP LTFGGGTKEIK	SEQ ID NO: 22
61289 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSSWIHWVRQAPGQGLEW MGLIDPSDSYTNYNQKFRGRVTMTVD TSTSTAYMELSSLRSEDTAVYY CASSDPHGGWGQGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG	SEQ ID NO: 23
61289 VL+CL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITMLS WYLQKPGQSPQL LIYQMSNLASGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQSLELP LTFGGGTKEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 24
61275 CDR-H1	YTFTSSWIH	SEQ ID NO: 25
61275 CDR-H2	LIDPSDSYTNYNQKFRG	SEQ ID NO: 26
61275 CDR-H3	ASSAPTGG	SEQ ID NO: 27
61275 CDR-L1	RSSKSLHSSGITYLS	SEQ ID NO: 28
61275 CDR-L2	QMSNLAS	SEQ ID NO: 29
61275 CDR-L3	AQALELPLT	SEQ ID NO: 30
61275 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSSWIHWVRQAPGQGLEW MGLIDPSDSYTNYNQKFRGRVTMTVD TSTSTAYMELSSLRSEDTAVYY CASSAPTGGWGQGTTTVTVSS	SEQ ID NO: 31
61275 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 32
61275 CL	RTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSP	SEQ ID NO: 33

	VTKSFNRGEC	
61275 VL	DIVMTQSPLSLPVTGPGEPAISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQALELP LTFGGGTKEIK	SEQ ID NO: 34
61275 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSSWIHWVRQAPGQGLEW MGLIDPSDSYTNYNQKFRGRVTMTVDTSTSTAYMELSSLRSEDTAVYY CASSAPTGGWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG	SEQ ID NO: 35
61275 VL+CL	DIVMTQSPLSLPVTGPGEPAISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQALELP LTFGGGTKEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 36
61278 CDR-H1	YTFTSYWIH	SEQ ID NO: 37
61278 CDR- H2	LIDPSDSYTNYNQKFRG	SEQ ID NO: 38
61278 CDR- H3	ASSDATGG	SEQ ID NO: 39
61278 CDR- L1	RSSKSLHSSGITYLS	SEQ ID NO: 40
61278 CDR- L2	QMSNLAS	SEQ ID NO: 41
61278 CDR- L3	AQALELPLT	SEQ ID NO: 42
61278 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWIHWVRQAPGQGLE WMGLIDPSDSYTNYNQKFRGRVTMTVDTSTSTAYMELSSLRSEDTAVY YCASSDATGGWGQGTTVTVSS	SEQ ID NO: 43
61278 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 44
61278 CL	RTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	SEQ ID NO: 45
61278 VL	DIVMTQSPLSLPVTGPGEPAISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQALELP LTFGGGTKEIK	SEQ ID NO: 46
61278 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWIHWVRQAPGQGLE WMGLIDPSDSYTNYNQKFRGRVTMTVDTSTSTAYMELSSLRSEDTAVY YCASSDATGGWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG	SEQ ID NO: 47
61278 VL+CL	DIVMTQSPLSLPVTGPGEPAISCRSSKSLHSSGITYLSWYLQKPGQSPQL	SEQ ID

	LIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQALELP LTFGGGKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC	NO: 48
61285 CDR-H1	YTFTSSWIH	SEQ ID NO: 49
61285 CDR-H2	LIDPSDSYTNYNQKFRG	SEQ ID NO: 50
61285 CDR-H3	ASSDPHGG	SEQ ID NO: 51
61285 CDR-L1	RSSKSLHSSGITYLS	SEQ ID NO: 52
61285 CDR-L2	QMSNLAG	SEQ ID NO: 53
61285 CDR-L3	AQSLELPLT	SEQ ID NO: 54
61285 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSSWIHWVRQAPGQGLEW MGLIDPSDSYTNYNQKFRGRVTMTVDTSTSTAYMELSSLRSEDTAVYY CASSDPHGGWGQGTTTVTVSS	SEQ ID NO: 55
61285 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 56
61285 CL	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	SEQ ID NO: 57
61285 VL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQSLELP LTFGGGKVEIK	SEQ ID NO: 58
61285 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSSWIHWVRQAPGQGLEW MGLIDPSDSYTNYNQKFRGRVTMTVDTSTSTAYMELSSLRSEDTAVYY CASSDPHGGWGQGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG	SEQ ID NO: 59
61285 VL+CL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQSLELP LTFGGGKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 60
61273 CDR-H1	YTFTSTWIH	SEQ ID NO: 61
61273 CDR-H2	LIDPSDSYTNYNQKFRG	SEQ ID NO: 62
61273 CDR-H3	ASSKPTGG	SEQ ID NO: 63
61273 CDR-L1	RSSKSLHSSGITYIS	SEQ ID NO: 64
61273 CDR-L2	QMSNLAG	SEQ ID NO: 65
61273	AQNLELPLT	SEQ ID

CDR-L3		NO: 66
61273 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSTWIHWVRQAPGQGLEWMGLIDPSDSYTNYNQKFRGRVTMTVDTSTSTAYMELSSLRSEDTAVYYCASSKPTGGWGQGTTVTVSS	SEQ ID NO: 67
61273 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 68
61273 CL	RTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 69
61273 VL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYISWYLQKPGQSPQLLIYQMSNLASGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLELPLTFGGGTKEIK	SEQ ID NO: 70
61273 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSTWIHWVRQAPGQGLEWMGLIDPSDSYTNYNQKFRGRVTMTVDTSTSTAYMELSSLRSEDTAVYYCASSKPTGGWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 71
61273 VL+CL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYISWYLQKPGQSPQLLIYQMSNLASGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLELPLTFGGGTKEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 72
60183 CDR-H1	YTFTSTWIH	SEQ ID NO: 73
60183 CDR- H2	LIDPSDSYTNYNQKFRG	SEQ ID NO: 74
60183 CDR-H3	ASSKPTGG	SEQ ID NO: 75
60183 CDR-L1	RSSKSLHSSGITYLS	SEQ ID NO: 76
60183 CDR-L2	QMSNLAS	SEQ ID NO: 77
60183 CDR-L3	AQNLELPLT	SEQ ID NO: 78
60183 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSTWIHWVRQAPGQGLEWMGLIDPSDSYTNYNQKFRGRVTMTVDTSTSTAYMELSSLRSEDTAVYYCASSKPTGGWGQGTTVTVSS	SEQ ID NO: 79
60183 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 80
60183 CL	RTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 81
60183	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQSPQL	SEQ ID

VL	LIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLELP LTFGGGKVEIK	NO: 82
60183 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSTWIHWVRQAPGQGLEW MGLIDPSDSYTNYNQKFRGRVTMTVDSTSTAYMELSSLRSEDTAVYY CASSKPTGGWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG	SEQ ID NO: 83
60183 VL+CL	DIVMTQSPLSLPVTGPGEPAISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLELP LTFGGGKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSITYLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 84
61283 CDR-H1	YTFTSAWIH	SEQ ID NO: 85
61283 CDR- H2	LIDPSDSYTNYNQKFRG	SEQ ID NO: 86
61283 CDR-H3	ASSDPYGG	SEQ ID NO: 87
61283 CDR-L1	RSSKSLHSSGITYLS	SEQ ID NO: 88
61283 CDR-L2	QMSNKAS	SEQ ID NO: 89
61283 CDR-L3	AQSLELPLT	SEQ ID NO: 90
61283 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSAWIHWVRQAPGQGLE WMGLIDPSDSYTNYNQKFRGRVTMTVDSTSTAYMELSSLRSEDTAVY YCASSDPYGGWGQGTTVTVSS	SEQ ID NO: 91
61283 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 92
61283 CL	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSITYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	SEQ ID NO: 93
61283 VL	DIVMTQSPLSLPVTGPGEPAISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNKASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQSLELP LTFGGGKVEIK	SEQ ID NO: 94
61283 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSAWIHWVRQAPGQGLE WMGLIDPSDSYTNYNQKFRGRVTMTVDSTSTAYMELSSLRSEDTAVY YCASSDPYGGWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG	SEQ ID NO: 95
61283	DIVMTQSPLSLPVTGPGEPAISCRSSKSLHSSGITYLSWYLQKPGQSPQL	SEQ ID

VL+CL	LIYQMSNKA SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQSLLELP LTFGGGKVEIKQVQLVQSGAEVKKPGASVKVSCKASGYTFTSAWIHW VRQAPGQGLEWMGLIDPSDSYTNYNQKFRGRVTMTVDTSTSTAYMEL SSLRSEDTAVYYCASSDPYGGWGQGT VTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFC SVMHEALHNHYTQKSLSLSPG	NO: 96
61286 CDR-H1	YTFTSTWIIH	SEQ ID NO: 97
61286 CDR- H2	LIDPSDSYTNYNQKFRG	SEQ ID NO: 98
61286 CDR-H3	ASSDLTGG	SEQ ID NO: 99
61286 CDR-L1	RSSKSLHSSGITYLS	SEQ ID NO: 100
61286 CDR-L2	QMSNLAS	SEQ ID NO: 101
61286 CDR-L3	AQALELPLT	SEQ ID NO: 102
61286 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSTWIIHWVRQAPGQGLEW MGLIDPSDSYTNYNQKFRGRVTMTVDTSTSTAYMELSSLRSEDTAVYY CASSDLTGGWGQGT VTVSS	SEQ ID NO: 103
61286 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSG VHTFPAVLQSSGLYSLSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFCSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 104
61286 CL	RTVAAPS VFIFPPSDEQIKSGTASVVCLINNFYPREAKVQWKVDNAIQ SGNSQESVTEQDSKDSYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	SEQ ID NO: 105
61286 VL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLASGVDPDRFSGSGSGTDFTSLKISRVEAEDVGVYYCAQALELP LTFGGGKVEIK	SEQ ID NO: 106
61286 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSTWIIHWVRQAPGQGLEW MGLIDPSDSYTNYNQKFRGRVTMTVDTSTSTAYMELSSLRSEDTAVYY CASSDLTGGWGQGT VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSVTVTPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCSVMHEALHNH YTQKSLSLSPG	SEQ ID NO: 107
61286 VL+CL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLASGVDPDRFSGSGSGTDFTSLKISRVEAEDVGVYYCAQALELP LTFGGGKVEIKRTVAAPS VFIFPPSDEQIKSGTASVVCLINNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSYLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 108
61279 CDR-H1	YTFKSYWIIH	SEQ ID NO: 109
61279 CDR- H2	LIDPSDSYTNYNQIFRG	SEQ ID NO: 110

61279 CDR-H3	ASSDATGG	SEQ ID NO: 111
61279 CDR-L1	RSSKSLHSSGITYLS	SEQ ID NO: 112
61279 CDR-L2	QMSNLAS	SEQ ID NO: 113
61279 CDR-L3	AQALELPLT	SEQ ID NO: 114
61279 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFKSYWIHWVRQAPGQGLE WMGLIDPSDSYTNYNQIFRGRVTMTVDSTSTAYMELSSLRSED TAVY YCASSDATGGWGQGT TTVTVSS	SEQ ID NO: 115
61279 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 116
61279 CL	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSYSLSSLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	SEQ ID NO: 117
61279 VL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQALELP LTFGGGT KVEIK	SEQ ID NO: 118
61279 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFKSYWIHWVRQAPGQGLE WMGLIDPSDSYTNYNQIFRGRVTMTVDSTSTAYMELSSLRSED TAVY YCASSDATGGWGQGT TTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG	SEQ ID NO: 119
61279 VL+CL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQALELP LTFGGGT KVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSYSLSSLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	SEQ ID NO: 120
56657 CDR-H1	YTFTSTWIH	SEQ ID NO: 121
56657 CDR- H2	LIDPSDSYTNYNQKFRG	SEQ ID NO: 122
56657 CDR-H3	ASSKPTGG	SEQ ID NO: 123
56657 CDR-L1	RSSKSLHSSGITYLS	SEQ ID NO: 124
56657 CDR-L2	QMSNLAS	SEQ ID NO: 125
56657 CDR-L3	AQNLELPLT	SEQ ID NO: 126
56657 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFKSYWIHWVRQAPGQGLE WIGLIDPSDSYTNYNQKFRGRATLTVDSTSTAYMELSSLRSED TAVYY CASSDPTGGWGQGT TTVTVSS	SEQ ID NO: 127
56657 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD	SEQ ID NO: 128

	VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNQKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	
56657 CL	RTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSSTLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFRNGEC	SEQ ID NO: 129
56657 VL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLASGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLPLP LTFGGGTKEIK	SEQ ID NO: 130
56657 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWIHWVRQAPGQGLE WIGLIDPSDSYTNYNQKFRGRATLTVDSTSTAYMELSSLRSEDTAVYY CASSDPTGGWGQGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQD WLNQKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG	SEQ ID NO: 131
56657 VL+CL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLASGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLPLP LTFGGGTKEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSSTLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFRNGEC	SEQ ID NO: 132
61255 CDR- H1	YTFTSYWIH	SEQ ID NO: 133
61255 CDR- H2	LIDPSDSYTNYNQKFRG	SEQ ID NO: 134
61255 CDR-H3	ASSDATGG	SEQ ID NO: 135
61255 CDR-L1	RSSKSLHSSGHTYLS	SEQ ID NO: 136
61255 CDR-L2	QMSNIAS	SEQ ID NO: 137
61255 CDR-L3	AQALELPLT	SEQ ID NO: 138
61255 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWIHWVRQAPGQGLE WIGLIDPSDSYTNYNQKFRGRATLTVDSTSTAYMELSSLRSEDTAVYY CASSDATGGWGQGTTTVTVSS	SEQ ID NO: 139
61255 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNQKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 140
61255 CL	RTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSSTLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFRNGEC	SEQ ID NO: 141
61255 VL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGHTYLSWYLQKPGQPPQ LLIYQMSNLASGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQALEL PLTFGGGTKEIK	SEQ ID NO: 142
61255 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWIHWVRQAPGQGLE WIGLIDPSDSYTNYNQKFRGRATLTVDSTSTAYMELSSLRSEDTAVYY CASSDATGGWGQGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP	SEQ ID NO: 143

	PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSEFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	
61255 VL+CL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQPPQLLIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQALELPLTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 144
60140 CDR-H1	YTFTSVWIH	SEQ ID NO: 145
60140 CDR-H2	LIDPSDSYTNYNQKFRG	SEQ ID NO: 146
60140 CDR-H3	ASSRPTGG	SEQ ID NO: 147
60140 CDR-L1	RSSKSLHSSGITYLS	SEQ ID NO: 148
60140 CDR-L2	QMSNLAG	SEQ ID NO: 149
60140 CDR-L3	AQNLELPLT	SEQ ID NO: 150
60140 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSVWIHWVRQAPGQGLEWIGLIDPSDSYTNYNQKFRGRATLTVDSTSTAYMELSSLRSEDTAVYYCASSRPTGGWGQGTTVTYSS	SEQ ID NO: 151
60140 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSEFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 152
60140 CL	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 153
60140 VL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQSPQLLIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLELPLTFGGGTKEIK	SEQ ID NO: 154
60140 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSVWIHWVRQAPGQGLEWIGLIDPSDSYTNYNQKFRGRATLTVDSTSTAYMELSSLRSEDTAVYYCASSRPTGGWGQGTTVTYSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSEFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 155
60140 VL+CL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQSPQLLIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLELPLTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 156
60143 CDR-H1	YTFTSTWIH	SEQ ID NO: 157
60143 CDR-H2	LIDPSDSYTNYNQKFRG	SEQ ID NO: 158
60143 CDR-	ASSKPTGG	SEQ ID

H3		NO: 159
60143 CDR-L1	RSSKSLHSSGITYLS	SEQ ID NO: 160
60143 CDR-L2	QMSNLAS	SEQ ID NO: 161
60143 CDR-L3	AQNLELPLT	SEQ ID NO: 162
60143 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSTWIHWVRQAPGQGLEWIGLIDPSDSYTNYNQKFRGRATLTVDSTSTAYMELSSLRSEDNAVYYCASSKPTGGWGQGTTVTVSS	SEQ ID NO: 163
60143 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 164
60143 CL	RTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 165
60143 VL	DIVMTQSPSLPVTGPGEPAISCRSSKSLHSSGITYLSWYLQKPGQSPQLLIYQMSNLASGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLELPLTFGGGTKVEIK	SEQ ID NO: 166
60143 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSTWIHWVRQAPGQGLEWIGLIDPSDSYTNYNQKFRGRATLTVDSTSTAYMELSSLRSEDNAVYYCASSKPTGGWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 167
60143 VL+CL	DIVMTQSPSLPVTGPGEPAISCRSSKSLHSSGITYLSWYLQKPGQSPQLLIYQMSNLASGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLELPLTFGGGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 168
61264 CDR-H1	YTFTSTWIH	SEQ ID NO: 169
61264 CDR-H2	LIDPSDSYTNYNQKFVG	SEQ ID NO: 170
61264 CDR-H3	ASSLPTGG	SEQ ID NO: 171
61264 CDR-L1	RSSKSLHSSGITYLS	SEQ ID NO: 172
61264 CDR-L2	QMSNLAS	SEQ ID NO: 173
61264 CDR-L3	AQQLELPLT	SEQ ID NO: 174
61264 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSTWIHWVRQAPGQGLEWIGLIDPSDSYTNYNQKFVGRATLTVDSTSTAYMELSSLRSEDNAVYYCASSLPTGGWGQGTTVTVSS	SEQ ID NO: 175
61264 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN	SEQ ID NO: 176

	QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	
61264 CL	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	SEQ ID NO: 177
61264 VL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQQLELP LTFGGGTKEIK	SEQ ID NO: 178
61264 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSTWIHWVRQAPGGGLEW IGLIDPSDSYTNYNQKFVGRATLTVDSTSTAYMELSSLRSEDTAVYYC ASSLPTGGWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPG	SEQ ID NO: 179
61264 VL+CL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQQLELP LTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 180
60130 CDR- H1	YTFTSVWIH	SEQ ID NO: 181
60130 CDR- H2	LIDPSDSYTNYNQKFR	SEQ ID NO: 182
60130 CDR- H3	ASSQPTGG	SEQ ID NO: 183
60130 CDR- L1	RSSKSLHSSGITYLS	SEQ ID NO: 184
60130 CDR- L2	QMSNLAG	SEQ ID NO: 185
60130 CDR- L3	AQNLELPLT	SEQ ID NO: 186
60130 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSVWIHWVRQAPGGGLE WIGLIDPSDSYTNYNQKFRGRATLTVDSTSTAYMELSSLRSEDTAVYY CASSQPTGGWGQGTTVTVSS	SEQ ID NO: 187
60130 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 188
60130 CL	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	SEQ ID NO: 189
60130 VL	DIVMTQSPLSLPVTPGEPASISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLELP LTFGGGTKEIK	SEQ ID NO: 190
60130 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSVWIHWVRQAPGGGLE WIGLIDPSDSYTNYNQKFRGRATLTVDSTSTAYMELSSLRSEDTAVYY CASSQPTGGWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA	SEQ ID NO: 191

	KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG	
60130 VL+CL	DIVMTQSPLSLPVTGPGEPAISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLELP LTFGGGKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 192
61286 CDR- H1	YTFTSTWIH	SEQ ID NO: 193
61286 CDR- H2	LIDPSDSYTNYNQKFR	SEQ ID NO: 194
61286 CDR-H3	ASSDLTGG	SEQ ID NO: 195
61286 CDR-L1	RSSKSLHSSGITYLS	SEQ ID NO: 196
61286 CDR- L2	QMSNLAG	SEQ ID NO: 197
61286 CDR- L3	AQALELPLT	SEQ ID NO: 198
61286 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSTWIHWVRQAPGQGLEW MGLIDPSDSYTNYNQKFRGRVTMTVDSTSTAYMELSSLRSEDVAVYY CASSDLTGGWGQGTTTVTVSS	SEQ ID NO: 199
61286 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 200
61286 CL	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	SEQ ID NO: 201
61286 VL	DIVMTQSPLSLPVTGPGEPAISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQALELP LTFGGGKVEIK	SEQ ID NO: 202
61286 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSTWIHWVRQAPGQGLEW MGLIDPSDSYTNYNQKFRGRVTMTVDSTSTAYMELSSLRSEDVAVYY CASSDLTGGWGQGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG	SEQ ID NO: 203
61286 VL+CL	DIVMTQSPLSLPVTGPGEPAISCRSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQALELP LTFGGGKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 204
61259 CDR- H1	YRFTSYWIH	SEQ ID NO: 205
61259 CDR- H2	LIDPSDSYTNYNQKFRG	SEQ ID NO: 206
61259 CDR-H3	ASSDATGG	SEQ ID NO: 207
61259	VSSKSLHSSGITYLS	SEQ ID

CDR-L1		NO: 208
61259 CDR-L2	QMSNLGS	SEQ ID NO: 209
61259 CDR-L3	AQALELPLT	SEQ ID NO: 210
61259 VH	QVQLVQSGAEVKKPGASVKVSCKASGYRFTSYWIHWVRQAPGQGLE WIGLIDPSDSYTNYNQKFRGRATLTVDSTSTAYMELSSLRSED TAVYY CASSDATGGWGQGTTTVTVSS	SEQ ID NO: 211
61259 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 212
61259 CL	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNFPYPREAKVQWKVDNALQ SGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	SEQ ID NO: 213
61259 VL	DIVMTQSPLSLPVTPGEPASISCVSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLGSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQALELP LTFGGGTKEIK	SEQ ID NO: 214
61259 VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYRFTSYWIHWVRQAPGQGLE WIGLIDPSDSYTNYNQKFRGRATLTVDSTSTAYMELSSLRSED TAVYY CASSDATGGWGQGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YTQKSLSLSPG	SEQ ID NO: 215
61259 VL+CL	DIVMTQSPLSLPVTPGEPASISCVSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLGSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQALELP LTFGGGTKEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNFPYPREAKVQWKVDNALQ SGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	SEQ ID NO: 216
60136 CDR-H1	YTHTSYWIH	SEQ ID NO: 217
60136 CDR-H2	LIDPSDSYTNYNQKFR	SEQ ID NO: 218
60136 CDR-H3	ASSRPTGG	SEQ ID NO: 219
60136 CDR-L1	RSSKSLHSSGITYLS	SEQ ID NO: 220
60136 CDR-L2	QMSNLAS	SEQ ID NO: 221
60136 CDR-L3	AQNLELPLT	SEQ ID NO: 222
60136 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTHTSYWIHWVRQAPGQGLE WIGLIDPSDSYTNYNQKFRGRATLTVDSTSTAYMELSSLRSED TAVYY CASSRPTGGWGQGTTTVTVSS	SEQ ID NO: 223
60136 CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL	SEQ ID NO: 224

		TVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG	
60136	CL	RTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 225
60136	VL	DIVMTQSPLSLPVTGPGEPAISCRSSKSLHSSGITYLSWYLQKPGQSPQLLIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLELPLTFGGGKVEIK	SEQ ID NO: 226
60136	VH+CH	QVQLVQSGAEVKKPGASVKVSCKASGYTHSTSYWIHWVRQAPGQGLEWIGLIDPSDSYTNYNQKFRGRATLTVDSTSTAYMELSSLRSEDTAVYYCASSRPTGGWGQGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 227
60136	VL+CL	DIVMTQSPLSLPVTGPGEPAISCRSSKSLHSSGITYLSWYLQKPGQSPQLLIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLELPLTFGGGKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 228
61267	CDR-H1	YTFTEYWIH	SEQ ID NO: 229
61267	CDR-H2	LIDPSDSYTNYNQRF	SEQ ID NO: 230
61267	CDR-H3	ASSDATGG	SEQ ID NO: 231
61267	CDR-L1	HSSKSLHSSGITYLS	SEQ ID NO: 232
61267	CDR-L2	QMSNLAG	SEQ ID NO: 233
61267	CDR-L3	AQSLELPLT	SEQ ID NO: 234
61267	VH	QVQLVQSGAEVKKPGASVKASCKASGYTFTEYWIHWVRQAPGQGLEWIGLIDPSDSYTNYNQRFGRATLTVDSTSTAYMELSSLRSEDTAVYYCASSDATGGWGQGTTTVTVSS	SEQ ID NO: 235
61267	CH	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG	SEQ ID NO: 236
61267	CL	RTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 237
61267	VL	DIVMTQSPLSLPVTGPGEPAISCHSSKSLHSSGITYLSWYLQKPGQSPQLLIYQMSNLAGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQSLELPLTFGGGKVEIK	SEQ ID NO: 238
61267	VH+CH	QVQLVQSGAEVKKPGASVKASCKASGYTFTEYWIHWVRQAPGQGLEWIGLIDPSDSYTNYNQRFGRATLTVDSTSTAYMELSSLRSEDTAVYYCASSDATGGWGQGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE	SEQ ID NO: 239

	NNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG	
61267 VL+CL	DIVMTQSPLSLPVTGPGEASISCHSSKSLHSSGITYLSWYLQKPGQSPQL LIYQMSNLAGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQSLELP LTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVY ACEVTHQGLSPVTKSFNRGEC	SEQ ID NO: 240
Human fibrin γ377-395 (Human P2 peptide)	YSMKKTTMKIIPFNRLTIG	SEQ ID NO: 241
60143 Light Chain	ATGACTAGGCTGACCGTGCTGGCCCTGCTTGCCGGACTCTTGGCCTC CTCGAGAGCGGATATTGTGATGACTCAGAGCCCACTCTCCCTGCCCCG TGACTCCTGGGGAACCCGCCTCGATCAGCTGTAGATCGTCCAAGTCA CTTCTCCACTCGTCCGGGATCACCTACCTGTCTGTTATTTGCAAAA GCCAGGACAGAGCCCGCAGCTCCTCATCTACCAAATGAGCAACCTG GCTTCCGGTGCTCCCGGATCGGTTCTCGGGGTCCGGATCTGGCACC GATTACGCTGAAAATTTCCCGCTGGAAGCCGAGGACGTGGGAGTG TACTACTGCGCACAAAACCTGGAAGTGCCTGACCTTCGGTGGCGG CACTAAGGTCGAAATCAAGCGGACCGTGGCAGCTCCGTCCGTGTTT ATCTTCCCGCTTCCGACGAGCAGCTGAAGTCCGGAACCGCCTCCGT CGTGTGCTGCTCAACAACCTTTTACCTCGCGAGGCCAAGGTCCAGT GGAAGGTCGATAACGCGCTGCAGAGCGGAAATAGCCAGGAGAGCG TGACCGAGCAGGACTCCAAGGACTCAACCTACTCACTGAGCTCCAC TCTGACCCTGTCAAAGGCGGACTACGAGAAGCACAAAGTGACGCC TGCGAAGTGACACATCAGGGCCTGTCCAGTCCCGTGACCAAGTCCTT CAACCGGGCGAATGCTAG	SEQ ID NO: 242
60143 Heavy Chain	ATGACCCGGCTGACCGTGCTGGCCCTCCTGGCTGGACTGCTGGCCTC CTCAAGAGCCCAGGTCCAGCTGGTGCAATCCGGCGCCGAAGTCAAG AAGCCAGGCGCAAGCGTGAAAGTGTGATGCAAAGCCTCCGGATACA CCTTCACCTCCACCTGGATTCACTGGGTGAGACAGGCCCGCGGTCAA GGACTGGAATGGATCGGGCTGATCGACCCGTCCGACTCGTACACCA ACTACAATCAGAAGTTTCGCGGTCCGGCTACTCTCACTGTGGATACC TCGACCTCCACCGCTTACATGGAAGTGTGATCGCTGCGGTCCGAGGA TACCGCCGTGTACTATTGCGCGTCTCCAAGCCGACTGGCGGATGGG GACAGGGAAGTACTGTGACGGTGTCTCCGCCTCGACCAAGGGCCC CTCCGTGTTTCCACTGGCCCCCTCATCCAAGTCTACCAGCGGAGGAA CCGACGCCCTAGGCTGTCTCGTGAAGGACTACTTCCCCGAGCCGGTC ACTGTCTCCTGGAAGTCCGGAGCCCTCACTAGCGGTGTCCACACTTT CCCGGCGGTGTTGCAAAGCTCCGGGCTGTACTCCCTGTCTCGGTGCG TCACCGTGCCGTCAAGCTCCCTCGGGACCCAGACATACATCTGTAAC GTCAACCATAAGCCATCCAACACCAAGTGGACAAGAAAGTGGAGC CGAAAAGCTGCGACAAGACTCACACTTGCCCTCCTTGCCCTGCACCC GAGCTTCTCGGAGGTCCCAGCGTGTCTCTGTTCCCGCCGAAGCCAA GGACACTCTGATGATTAGCCGCACTCCTGAGGTCACTGTGTCTGTTG TGGACGTGTCCCATGAGGACCCTGAAGTCAAGTTCAATTGGTACGTG GACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCGAGGGAGGAG CAGTACAACCTCGACCTATCGCGTGGTGTCCGTGCTCACCGTGTGCA TCAGGATTGGCTGAACGGGAAGGAGTATAAGTGCAAAGTGTCCAAC AAGGCTTTGCCGGCCCCCTATCGAAAAGACCATTAGCAAGGCCAAGG GGACCCAAGGGAGCCTCAAGTGTACACCCTGCCGCTTCGAGAGA TGAAGTGAACCAAGAACCAAGTGTCCCTCACGTGCCTCGTGAAGGGC TTCTACCCCTCCGATATCGCGGTGGAATGGGAATCCAACGGACAGC CCGAAAACAACACTACAAGACCACCCCTCCGGTGCTTGATAGCGACGG CTCGTCTCTCTGTAACGAGCTGACAGTGGACAAGTCAAGGTGGC AGCAGGGCAACGTGTTCTCATGCTCCGTGATGCACGAAGCGTTGCA CAATCACTACACCCAGAAGTCCGCTTAGCCTGAGCCCTGGATAG□□	SEQ ID NO: 243
60143- A234LA235L	ATGACTAGGCTGACCGTGCTGGCCCTGCTTGCCGGACTCTTGGCCTC CTCGAGAGCGGATATTGTGATGACTCAGAGCCCACTCTCCCTGCCCCG	SEQ ID NO: 244

Light Chain	TGACTCCTGGGGAACCCGCCTCGATCAGCTGTAGATCGTCCAAGTCA CTTCTCCACTCGTCCGGGATCACCTACCTGTCTGGTATTTGCAAAA GCCAGGACAGAGCCCGCAGCTCCTCATCTACCAAATGAGCAACCTG GCTTCCGGTGTCCCGGATCGGTTCTCGGGGTCCGGATCTGGCACC CTTCACGCTGAAAATTTCCCGCGTGGAAGCCGAGGACGTGGGAGTG TACTACTGCGCACAAAACCTGGAAGTCCCTGACCTTCGGTGGCGG CACTAAGGTCGAAATCAAGCGGACCGTGGCAGCTCCGTCCGTGTTC ATCTTCCCGCCTTCCGACGAGCAGCTGAAGTCCGGAACCGCCTCCGT CGTGTGCCTGCTCAACAACCTTTTACCCTCGCGAGGCCAAGGTCCAGT GGAAGGTCGATAACCGCGCTGCAGAGCGGAAATAGCCAGGAGAGCG TGACCGAGCAGGACTCCAAGGACTCAACCTACTCACTGAGCTCCAC TCTGACCCTGTCAAAGGCGGACTACGAGAAGCACAAAGTGTACGCC TGCGAAGTGACACATCAGGGCCTGTCCAGTCCCGTGACCAAGTCCTT CAACCGGGGCGAATGCTAG□	
60143- A234LA235L Heavy Chain	ATGACCCGGCTGACCGTGCTGGCCCTCCTGGCTGGACTGCTGGCCTC CTCAAGAGCCCAGGTCCAGCTGGTGCAATCCGGCGCCGAAGTCAAG AAGCCAGGCGCAAGCGTGAAAGTGTATGCAAAGCCTCCGGATACA CCTTCACCTCCACCTGGATTCACTGGGTGACACAGGCCCGCGTCAA GGACTGGAATGGATCGGGCTGATCGACCCGTCCGACTCGTACACCA ACTACAATCAGAAGTTTCGCGGTCCGGCTACTCTCACTGTGGATACC TCGACCTCCACCGCTTACATGGAAGTGTATCGCTGCGGTCCGAGGA TACCGCCGTGTACTATTGCGCGTCTCCAAGCCGACTGGCGGATGGG GACAGGGAAGTACTGTGACGGTGTCTCCGCCTCGACCAAGGGCCC CTCCGTGTTTCCACTGGCCCCCTCATCCAAGTCTACCAGCGGAGGAA CCGACAGCCCTAGGCTGTCTCGTGAAGGACTACTTCCCCGAGCCGGT ACTGTCTCCTGGAAGTCCGGAGCCCTCACTAGCGGTGTCCACACTTT CCCGGCGGTGTTGCAAAGCTCCGGGCTGTACTCCCTGTCTCGGTCTG TCACCGTGCCGTCAAGCTCCCTCGGGACCCAGACATACATCTGTAAC GTCAACCATAAGCCATCCAACACCAAAGTGGACAAGAAAGTGGAGC CGAAAAGCTGCGACAAGACTCACACTTGCCCTCCTTGCCCTGCACCC GAGGCAGCAGGAGGTCCAGCGTGTTCCTGTTCCCGCCGAAGCCCA AGGACACTCTGATGATTAGCCGCACTCCTGAGGTACCTGTGTCTGTG GTGGACGTGTCCCATGAGGACCCTGAAGTCAAGTTCAATTGGTACGT GGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCGAGGAGGA GCAGTACAAGTTCGACCTATCGCGTGGTGTCCGTGCTACCGTGCTGC ATCAGGATTGGCTGAACGGGAAGGAGTATAAGTGCAAAGTGTCCAA CAAGGCTTTGCCGGCCCCCTATCGAAAAGACCATTAGCAAGGCCAAG GGGCAGCCAAGGGAGCCTCAAGTGTACACCCTGCCGCCTTCGAGAG ATGAACTGACCAAGAACCAAGTGTCCCTCACGTGCCTCGTGAAGGG CTTCTACCCCTCCGATATCGCGGTGGAATGGGAATCCAACGGACAG CCCGAAAACAATAACAAGACCACCCCTCCGGTGCTTGATAGCGACG GCTCGTTCTTCTGTACTCGAAGCTGACAGTGGACAAGTACCGTGG CAGCAGGGCAACGTGTTCTCATGCTCCGTGATGCACGAAGCGTTGC ACAATCACTACACCCAGAAGTCGCTTAGCCTGAGCCCTGGATAG	SEQ ID NO: 245
5B8 Heavy Chain	QVQLQQPGAELVRPGTSVKLSCKASGYTFTSYWIHWVKQRPGGLEWI GLIDPSDSYTNYNQKFRGKATLTVDTSSSTAYMQLSSLTSEDSAVYYCA SSDPTGCWQGTTTLTVSSAKTTPPSVYPLAPGCGDITGSSVTSGLVKG YFPEPVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQTV TCSVAHPASSTTVDKKLEPSGPISINPCPPCKECHKCPAPNLEGGPSVFI FPPNIKDVLMISLTPKVTCTVVDVSEDDPDVQISWVFNNVVHTAQQT HREDYNSTIRVVSTLPIQHQDWMMSGKEFKCKVNNKDLPSPIERTISKIKG LVRAPQVYTLPPPAEQLSRKDVSLTCLVVGFNPGDISVEWTSNGHTEEN YKDTAPVLDSGSGYFIYSKLNMKTSKWEKTDSEFCNVRHEGLKNYYLK KTISRSPGK	SEQ ID NO: 246
5B8 Light Chain	RADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSRQ NGVLNSWTDQDSKDYMSSTLTLTKDEYERHNSYTCEATHKSTSP VKSFNRECDIVMTQAAFSNPITLGTASMSCRSSKSLHSSGITYLSWY LQKPGQSPQLLIYQMSNLAGVPPDRFSSSGSGTDFTLRISRVEAEDVGV	SEQ ID NO: 246

	YYCAQNLELPLTFGAGTKLELK	
THN227 Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWIHWVRQAPGQGLEW IGLIDPSDSYTNYNQKFRGRVTITRDSTSTAYMELSSLRSED TAVYYCA SSDPTGGWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVHLHQQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQ KSLSLSPGK	SEQ ID NO: 247
THN227 Light Chain	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGECDIVMTQAAFSNPVTPGTPASISCRSSKSLHSSGITYLSW YLQKPGQSPQLLIYQMSNLAGVDPDRFSSSGSGTDFTLKISRVEAEDVG VYYCAQNLELPLTFGQGQTKLEIK	SEQ ID NO: 248
Mouse/Rat P2 peptide	YSMKETTMKIIPFNRLSIG	SEQ ID NO: 249
Rabbit P2 peptide	YSMKKTTMKIPLNRLSIG	SEQ ID NO: 250
Human P2 peptide extended	TTMKIIPFNRLTIGEGQQHHLGGAKQVRP	SEQ ID NO: 251
Rat P2 peptide extended	TTMKIIPFNRLSIGDGQQHMHMGGSKQVS	SEQ ID NO: 252
Rabbit P2 peptide extended	TTMKIPLNRLSIGEGQQFHVGGAKQVRP	SEQ ID NO: 253

CLAIMS

1. An isolated antibody that binds human fibrin or fibrinogen γ C domain, comprising a heavy chain comprising a variable heavy (VH) chain sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a light chain comprising a variable light (VL) chain sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:
 - a. CDR-H1 comprises the sequence set forth in SEQ ID NO: 1, 13, 25, 37, 49, 61, 73, 85, 97, 109, 121, 133, 145, 157, 169, 181, 193, 205, 217, or 229;
 - b. CDR-H2 comprises the sequence set forth in SEQ ID NO: 2, 14, 26, 38, 50, 62, 74, 86, 98, 110, 122, 134, 146, 158, 170, 182, 194, 206, 218, or 230;
 - c. CDR-H3 comprises the sequence set forth in SEQ ID NO: 3, 15, 27, 39, 51, 63, 75, 87, 99, 111, 123, 135, 147, 159, 171, 183, 195, 207, 219, or 231;
 - d. CDR-L1 comprises the sequence set forth in SEQ ID NO: 4, 16, 28, 40, 52, 64, 76, 88, 100, 112, 124, 136, 148, 160, 172, 184, 196, 208, 220, or 232;
 - e. CDR-L2 comprises the sequence set forth in SEQ ID NO: 5, 17, 29, 41, 53, 65, 77, 89, 101, 113, 125, 137, 149, 161, 173, 185, 197, 209, 221, or 233; and
 - f. CDR-L3 comprises the sequence set forth in SEQ ID NO: 6, 18, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138, 150, 162, 174, 186, 198, 210, 222, or 234.
2. The isolated antibody of claim 1, wherein the antibody comprises a VH sequence selected from a sequence set forth in one of SEQ ID NOs: 7, 19, 31, 43, 55, 67, 79, 91, 103, 115, 127, 139, 151, 163, 175, 187, 199, 211, 223, or 235.
3. The isolated antibody of claim 1 or 2, wherein the antibody comprises a VL sequence selected from a sequence set forth in SEQ ID NO 10, 22, 34, 46, 58, 70, 82, 94, 106, 118, 130, 142, 154, 166, 178, 190, 202, 214, 226, or 238.
4. The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence selected from a sequence set forth in one of SEQ ID Nos: 7, and the VL sequence set forth in SEQ ID NO: 10.
5. The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 19 and a VL sequence set forth in SEQ ID NO: 22.

6. The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 31 and a VL sequence set forth in SEQ ID NO: 34.
7. The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 43 and a VL sequence set forth in SEQ ID NO: 46.
8. The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 55 and a VL sequence set forth in SEQ ID NO: 58.
9. The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 67 and a VL sequence set forth in SEQ ID NO: 70.
10. The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 79 and a VL sequence set forth in SEQ ID NO: 82.
11. The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 91 and a VL sequence set forth in SEQ ID NO: 94.
12. The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 103 and a VL sequence set forth in SEQ ID NO: 106.
13. The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 115 and a VL sequence set forth in SEQ ID NO: 118.
14. The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 127 and a VL sequence set forth in SEQ ID NO: 130.
15. The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 139 and a VL sequence set forth in SEQ ID NO: 142.
16. The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 151 and a VL sequence set forth in SEQ ID NO: 154.
17. The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 163 and a VL sequence set forth in SEQ ID NO: 166.

- 18.** The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 175 and a VL sequence set forth in SEQ ID NO: 178.
- 19.** The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 187 and a VL sequence set forth in SEQ ID NO: 190.
- 20.** The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 199 and a VL sequence set forth in SEQ ID NO: 202.
- 21.** The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 211 and a VL sequence set forth in SEQ ID NO: 214.
- 22.** The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 223 and a VL sequence set forth in SEQ ID NO: 226.
- 23.** The isolated antibody of any one of the above claims, wherein the antibody comprises a VH sequence set forth in SEQ ID NO: 235 and a VL sequence set forth in SEQ ID NO: 238.
- 24.** The isolated antibody of any one of the above claims, wherein the antibody comprises a humanized, human or chimeric antibody.
- 25.** The isolated antibody of claim 24, wherein the antibody comprises a humanized antibody.
- 26.** The isolated antibody of any one of the above claims, wherein the antibody comprises a heavy chain human constant region of a class selected from IgG, IgA, IgD, IgE, and IgM.
- 27.** The isolated antibody of any one of the above claims, wherein the human Fc region comprises a human heavy chain constant region of the class IgG and a subclass selected from IgG1, IgG2, IgG3, and IgG4.
- 28.** The isolated antibody of claim 27, wherein the human Fc region comprises wild-type, human IgG1 Fc.

- 29.** The isolated antibody of claim 28, wherein the human Fc domain comprises a sequence set forth in SEQ ID NO: 8, 20, 32, 44, 56, 68, 80, 92, 104, 116, 128, 140, 152, 164, 176, 188, 200, 212, 224, or 236.
- 30.** The isolated antibody of any one of the above claims, wherein the heavy chain comprises a constant heavy chain sequence set forth by SEQ ID NO: 8, 20, 32, 44, 56, 68, 80, 92, 104, 116, 128, 140, 152, 164, 176, 188, 200, 212, 224, or 236.
- 31.** The isolated antibody of any one of the above claims, wherein the light chain comprises a constant light chain sequence set forth by SEQ ID NO: 9, 21, 33, 45, 57, 69, 81, 93, 105, 117, 129, 141, 153, 165, 177, 189, 201, 213, 225, or 237.
- 32.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 7, and the VL sequence set forth in SEQ ID NO: 10; and the human Fc region comprises wild-type, human IgG1 Fc.
- 33.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 19, and the VL sequence set forth in SEQ ID NO: 22; and the human Fc region comprises wild-type, human IgG1 Fc.
- 34.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 31, and the VL sequence set forth in SEQ ID NO: 34; and the human Fc region comprises wild-type, human IgG1 Fc.
- 35.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 43, and the VL sequence set forth in SEQ ID NO: 46; and the human Fc region comprises wild-type, human IgG1 Fc.
- 36.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 55, and the VL sequence set forth in SEQ ID NO: 58; and the human Fc region comprises wild-type, human IgG1 Fc.
- 37.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 67, and the VL sequence set forth in SEQ ID NO: 70; and the human Fc region comprises wild-type, human IgG1 Fc.
- 38.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 79, and the VL sequence set forth in SEQ ID NO: 82; and the human Fc region comprises wild-type, human IgG1 Fc.

- 39.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 91, and the VL sequence set forth in SEQ ID NO: 94; and the human Fc region comprises wild-type, human IgG1 Fc.
- 40.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 103, and the VL sequence set forth in SEQ ID NO: 106; and the human Fc region comprises wild-type, human IgG1 Fc.
- 41.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 115, and the VL sequence set forth in SEQ ID NO: 118; and the human Fc region comprises wild-type, human IgG1 Fc.
- 42.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 127, and the VL sequence set forth in SEQ ID NO: 130; and the human Fc region comprises wild-type, human IgG1 Fc.
- 43.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 139, and the VL sequence set forth in SEQ ID NO: 142; and the human Fc region comprises wild-type, human IgG1 Fc.
- 44.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 151, and the VL sequence set forth in SEQ ID NO: 154; and the human Fc region comprises wild-type, human IgG1 Fc.
- 45.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 163, and the VL sequence set forth in SEQ ID NO: 166; and the human Fc region comprises wild-type, human IgG1 Fc.
- 46.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 175, and the VL sequence set forth in SEQ ID NO: 178; and the human Fc region comprises wild-type, human IgG1 Fc.
- 47.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 187, and the VL sequence set forth in SEQ ID NO: 190; and the human Fc region comprises wild-type, human IgG1 Fc.
- 48.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 199, and the VL sequence set forth in SEQ ID NO: 202; and the human Fc region comprises wild-type, human IgG1 Fc.

- 49.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 211, and the VL sequence set forth in SEQ ID NO: 214; and the human Fc region comprises wild-type, human IgG1 Fc.
- 50.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 223, and the VL sequence set forth in SEQ ID NO: 226; and the human Fc region comprises wild-type, human IgG1 Fc.
- 51.** The isolated antibody of any one of the above claims, wherein the antibody comprises the VH sequence set forth in SEQ ID NO: 235, and the VL sequence set forth in SEQ ID NO: 238; and the human Fc region comprises wild-type, human IgG1 Fc.
- 52.** The isolated antibody of any one of claims 27 - 51, wherein the Fc region comprises one or more amino acid substitutions, wherein the one or more substitutions result in increased antibody half-life, increased ADCC activity, increased ADCP activity, or increased CDC activity compared with the Fc without the one or more substitutions.
- 53.** The isolated antibody of any one of the above claims, wherein the Fc region binds an Fc γ Receptor selected from the group consisting of: Fc γ RI, Fc γ RIIa, Fc γ RIIb, Fc γ RIIc, Fc γ RIIIa, and Fc γ RIIIb.
- 54.** The isolated antibody of any one of the above claims, wherein the antibody comprises a monoclonal antibody.
- 55.** The antibody of claim 1, wherein the antibody binds an γ 377-395 epitope of the fibrin or fibrinogen γ C domain.
- 56.** The isolated antibody of any one of the above claims, wherein the antibody binds to peptide comprising an amino acid sequence set forth in at least one of SEQ ID NOs: 241, and 249-253 with a K_D of less than or equal to about 1, 2, 3, 4, 5, 6, 7, or 8×10^{-5} M, as measured by surface plasmon resonance (SPR) single cycle kinetics (SCK) assay.
- 57.** The isolated antibody of any one of the above claims, wherein the antibody binds to a peptide comprising the sequence of the γ 377-395 epitope of the human fibrin or fibrinogen γ C domain with a K_D of less than or equal to about 8×10^{-5} M, as measured by surface plasmon resonance (SPR) single cycle kinetics (SCK) assay.
- 58.** The isolated antibody of any one of the above claims, wherein the antibody inhibits Mac-1 binding to fibrin or fibrinogen γ C domain.

59. The isolated antibody of any one of the above claims, wherein the antibody exhibits inhibition of microglial adhesion to the fibrin or fibrinogen γ C domain.
60. The isolated antibody of any one of the above claims, for use in the treatment of a degenerative disorder of the nervous system.
61. An isolated polynucleotide or set of polynucleotides encoding the antibody of any of the above claims, a VH thereof, a VL thereof, a light chain thereof, a heavy chain thereof, or an antigen-binding portion thereof; optionally cDNA.
62. A vector or set of vectors comprising the polynucleotide or set of polynucleotides of claim 61.
63. A host cell comprising the polynucleotide or set of polynucleotides of claim 61 or the vector or set of vectors of claim 62.
64. A method of producing an antibody, the method comprising expressing the antibody with the host cell of claim 63 and isolating the expressed antibody.
65. A pharmaceutical composition comprising the antibody of any one of claims 1 - 60 and a pharmaceutically acceptable excipient.
66. A kit comprising the antibody of any one of claims 1 - 60 or a pharmaceutical composition of claim 65 and instructions for use
67. A method for treating a degenerative disorder of the nervous system, the method comprising administering to a mammalian subject a therapeutically effective amount the antibody of any one of claims 1 - 60 or a pharmaceutical composition of claim 65.
68. The method of claim 67, wherein the degenerative disorder of the nervous system is selected from the group consisting of: multiple sclerosis, spinal cord injury, stroke, and Alzheimer's Disease.
69. A method for treating a pathology associated with Mac-1 binding to fibrin or Mac-1 binding with fibrinogen, the method comprising administering to a mammalian subject a therapeutically effective amount the antibody of any one of claims 1 - 60 or a pharmaceutical composition of claim 65.
70. A method of inhibiting microglia activation, the method comprising administering to a mammalian subject a therapeutically effective amount the antibody of any one of claims 1 - 60 or a pharmaceutical composition of claim 65.

71. A method of preventing a degenerative disorder of the nervous system, the method comprising administering to a mammalian subject a therapeutically effective amount the antibody of any one of claims 1 - 60 or a pharmaceutical composition of claim 65.
72. A method of treating colitis in a subject in need thereof, the method comprising administering to a mammalian subject a therapeutically effective amount the antibody of any one of claims 1 - 60 or a pharmaceutical composition of claim 65.
73. A method of preventing colitis in a subject in need thereof, the method comprising administering to a mammalian subject a therapeutically effective amount the antibody of any one of claims 1 - 60 or a pharmaceutical composition of claim 65.
74. An isolated antibody that binds human fibrin or fibrinogen γ C domain, wherein the antibody binds human fibrin at any one of amino acid residues Lys 411, Ile 412, Ile 413, Phe 415, Asn 416, Arg 417, Leu 418, Thr 419, Ile 420, and Gly 421.
75. The isolated antibody of claim 74, wherein the antibody binds human fibrin at at least two, three, four, five, six, seven, eight, nine, or all ten of amino acid residues Lys 411, Ile 412, Ile 413, Phe 415, Asn 416, Arg 417, Leu 418, Thr 419, Ile 420, and Gly 421.
76. The isolated antibody of claims 74 or 75, wherein the antibody comprises a VH region comprising a paratope that comprises any one of amino acid residues Ser 31, Tyr 32, Trp 33, His 35, Trp 47, Leu 50, Asp 52, Asp 54, Tyr 56, Ala 93, Ser 94, Ser 95, Lys 96 or Asp 96, Pro 97 or Ala 97, Gly 101, Gly102, and Trp 103.
77. The isolated antibody of claim 76, wherein the antibody comprises a VH region comprising a paratope that comprises at least two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, or all seventeen of amino acid residues Ser 31, Tyr 32, Trp 33, His 35, Trp 47, Leu 50, Asp 52, Asp 54, Tyr 56, Ala 93, Ser 94, Ser 95, Lys 96 or Asp 96, Pro 97 or Ala 97, Gly 101, Gly102, and Trp 103.
78. The isolated antibody of claim 77, wherein the antibody comprises a VH region comprising a paratope that comprises amino acid residues Ser 31, Trp 33, His 35, Asp 52, Asp 54, Tyr 56, Ser 94, Gly 101, Gly 102, and Trp 103.
79. The isolated antibody of claim 78, wherein the antibody comprises a VH region comprising a paratope that comprises amino acid residues Ser 31, Trp 33, His 35, Asp 52, Asp 54, Tyr 56, Ala 93, Ser 94, Lys 96, Pro 97, Gly 101, Gly102, and Trp 103.

- 80.** The isolated antibody of claim 78, wherein the antibody comprises a VH region comprising a paratope that comprises amino acid residues Ser 31, Tyr 32, Trp 33, His 35, Trp 47, Asp 52, Asp 54, Tyr 56, Ser 94, Ser 95, Asp 96, Ala 97, Gly 101, Gly102, and Trp 103.
- 81.** The isolated antibody of any one of claims 74-80, wherein the antibody comprises a VL region comprising a paratope that comprises any one of amino acid residues His 27, Tyr 32, Tyr 36, Leu 46, Tyr 49, Gln 50, Ala 91 or Asn 91, Leu 92, Leu 94, and Leu 96.
- 82.** The isolated antibody of claim 81, wherein the antibody comprises a VL region comprising a paratope that comprises at least two, three, four, five, six, seven, eight, nine or all ten amino acid residues His 27, Tyr 32, Tyr 36, Leu 46, Tyr 49, Gln 50, Ala 91 or Asn 91, Leu 92, Leu 94, and Leu 96.
- 83.** The isolated antibody of claim 82, wherein the antibody comprises a VL region comprising a paratope that comprises the amino acid residues His 27, Tyr 32, Tyr 36, Leu 46, Gln 50, Leu 92, Leu 94, and Leu 96.
- 84.** The isolated antibody of claim 83, wherein the antibody comprises a VL region comprising a paratope that comprises the amino acid residues His 27, Tyr 32, Tyr 36, Leu 46, Gln 50, Asn 91, Leu 92, Leu 94, and Leu 96.
- 85.** The isolated antibody of claim 83, wherein the antibody comprises a VL region comprising a paratope that comprises the amino acid residues His 27, Tyr 32, Tyr 36, Leu 46, Tyr 49, Gln 50, Ala 91, Leu 92, Leu 94, and Leu 96.
- 86.** The isolated antibody of any one of claims 74-85, wherein the antibody comprises a humanized, human or chimeric antibody.
- 87.** The isolated antibody of claim 86, wherein the antibody comprises a humanized antibody.
- 88.** The isolated antibody of any one of claims 74-87, wherein the antibody comprises a heavy chain human constant region of a class selected from IgG, IgA, IgD, IgE, and IgM.
- 89.** The isolated antibody of any one of claims 74-88, wherein the human Fc region comprises a human heavy chain constant region of the class IgG and a subclass selected from IgG1, IgG2, IgG3, and IgG4.

- 90.** The isolated antibody of claim 89, wherein the human Fc region comprises wild-type, human IgG1 Fc.
- 91.** The isolated antibody of claim 88, wherein the human Fc domain comprises a sequence set forth in SEQ ID NO: 8, 20, 32, 44, 56, 68, 80, 92, 104, 116, 128, 140, 152, 164, 176, 188, 200, 212, 224, or 236.
- 92.** The isolated antibody of any one of claims 74-91, wherein the Fc region comprises one or more amino acid substitutions, wherein the one or more substitutions result in increased antibody half-life, increased ADCC activity, increased ADCP activity, or increased CDC activity compared with the Fc without the one or more substitutions.
- 93.** The isolated antibody of any one of claims 74-92, wherein the Fc region binds an Fc γ Receptor selected from the group consisting of: Fc γ RI, Fc γ RIIa, Fc γ RIIb, Fc γ RIIc, Fc γ RIIIa, and Fc γ RIIIb.
- 94.** The isolated antibody of any one of claims 74-93, wherein the antibody comprises a monoclonal antibody.
- 95.** The isolated antibody of any one of claims 74-94, wherein the antibody binds to a peptide comprising an amino acid sequence set forth in at least one of SEQ ID NOs: 241, and 249-253 with a K_D of less than or equal to about 1, 2, 3, 4, 5, 6, 7, or 8×10^{-5} M, as measured by surface plasmon resonance (SPR) single cycle kinetics (SCK) assay.
- 96.** The isolated antibody of any one of claims 74-95, wherein the antibody binds to a peptide comprising the sequence of the γ 377-395 epitope of the human fibrin or fibrinogen γ C domain with a K_D of less than or equal to about 8×10^{-5} M, as measured by surface plasmon resonance (SPR) single cycle kinetics (SCK) assay.
- 97.** The isolated antibody of any one of claims 74-96, wherein the antibody inhibits Mac-1 binding to fibrin or fibrinogen γ C domain.
- 98.** The isolated antibody of any one of claims 74-97, wherein the antibody exhibits inhibition of microglial adhesion to the fibrin or fibrinogen γ C domain.
- 99.** The isolated antibody of any one of claims 74-98 for use in the treatment of a degenerative disorder of the nervous system.
- 100.** The isolated antibody of any one of claims 74-98 for use in the treatment of a condition associated with inflammation of the eye.

- 101.** The isolated antibody of claim 100, wherein the condition is uveitis.
- 102.** An isolated polynucleotide or set of polynucleotides encoding the antibody of any of claims 74-101, a VH thereof, a VL thereof, a light chain thereof, a heavy chain thereof, or an antigen-binding portion thereof; optionally cDNA.
- 103.** A vector or set of vectors comprising the polynucleotide or set of polynucleotides of claim 102.
- 104.** A host cell comprising the polynucleotide or set of polynucleotides of claim 61 or the vector or set of vectors of claim 103.
- 105.** A method of producing an antibody, the method comprising expressing the antibody with the host cell of claim 104 and isolating the expressed antibody.
- 106.** A pharmaceutical composition comprising the antibody of any one of claims 74-101 and a pharmaceutically acceptable excipient.
- 107.** A kit comprising the antibody of any one of claims 74-101 or a pharmaceutical composition of claim 106 and instructions for use
- 108.** A method for treating a degenerative disorder of the nervous system, the method comprising administering to a mammalian subject a therapeutically effective amount the antibody of any one of claims 74-101 or a pharmaceutical composition of claim 106.
- 109.** The method of claim 108, wherein the degenerative disorder of the nervous system is selected from the group consisting of: multiple sclerosis, spinal cord injury, stroke, and Alzheimer's Disease.
- 110.** A method for treating a pathology associated with Mac-1 binding to fibrin or Mac-1 binding with fibrinogen, the method comprising administering to a mammalian subject a therapeutically effective amount the antibody of any one of claims 74-101 or a pharmaceutical composition of claim 106.
- 111.** A method of inhibiting microglia activation, the method comprising administering to a mammalian subject a therapeutically effective amount the antibody of any one of claims 74-101 or a pharmaceutical composition of claim 106.
- 112.** A method of preventing a degenerative disorder of the nervous system, the method comprising administering to a mammalian subject a therapeutically effective amount the antibody of any one of claims 74-101 or a pharmaceutical composition of claim 106.

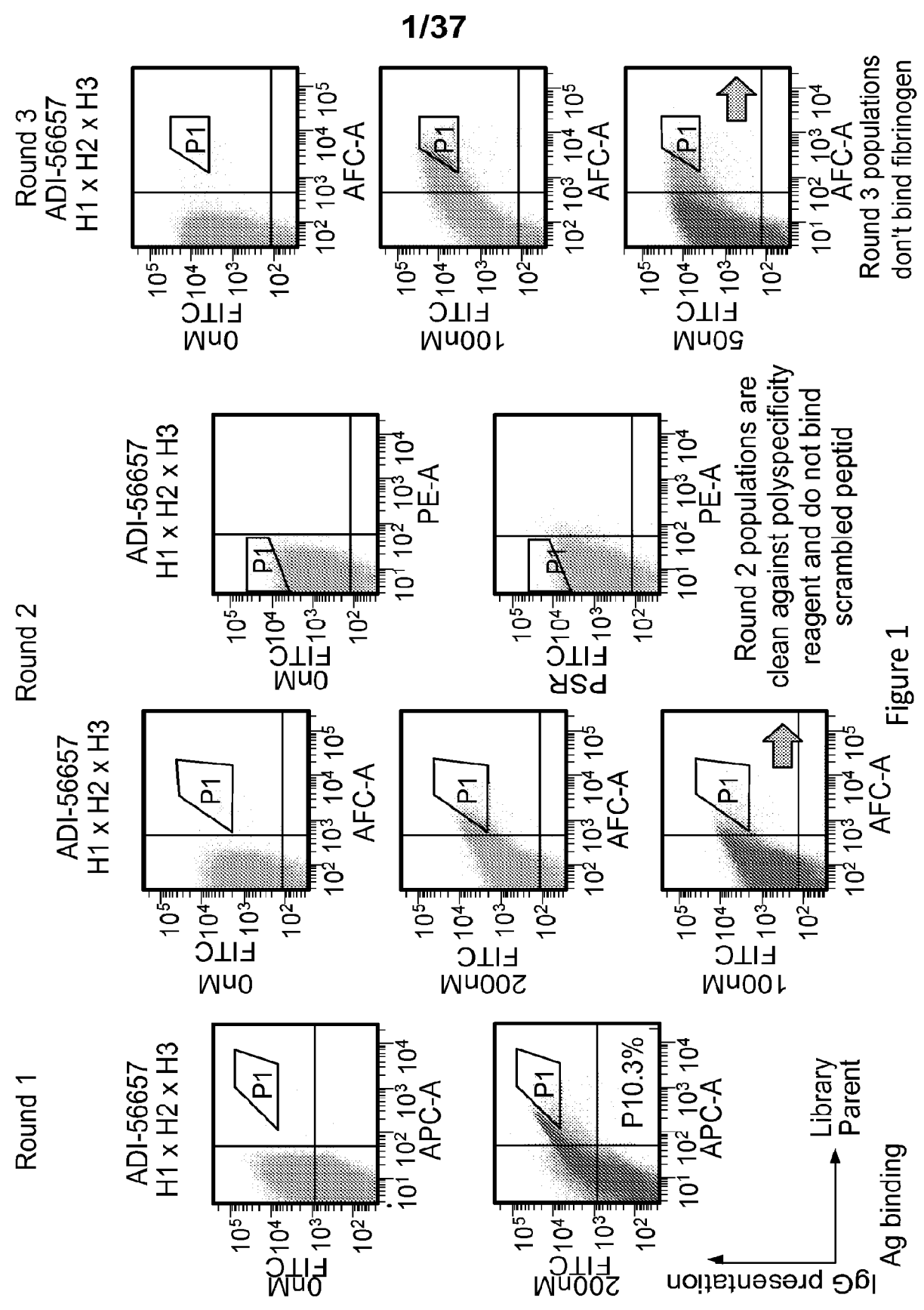
113. A method of treating colitis in a subject in need thereof, the method comprising administering to a mammalian subject a therapeutically effective amount the antibody of any one of claims 74-101 or a pharmaceutical composition of claim 106.

114. A method of preventing colitis in a subject in need thereof, the method comprising administering to a mammalian subject a therapeutically effective amount the antibody of any one of claims 74-101 or a pharmaceutical composition of claim 106.

115. A method of treating an inflammatory condition of the eye in a subject in need thereof, comprising administering to the subject the antibody of any one of claims 1-60, or 74-101 or a pharmaceutical composition of claim 65 or 106.

116. A method of preventing an inflammatory condition of the eye in a subject in need thereof, comprising administering to the subject the antibody of any one of claims 1-60, or 74-101 or a pharmaceutical composition of claim 65 or 106.

117. The method of claim 115 or claim 116, wherein the inflammatory condition of the eye comprises uveitis.



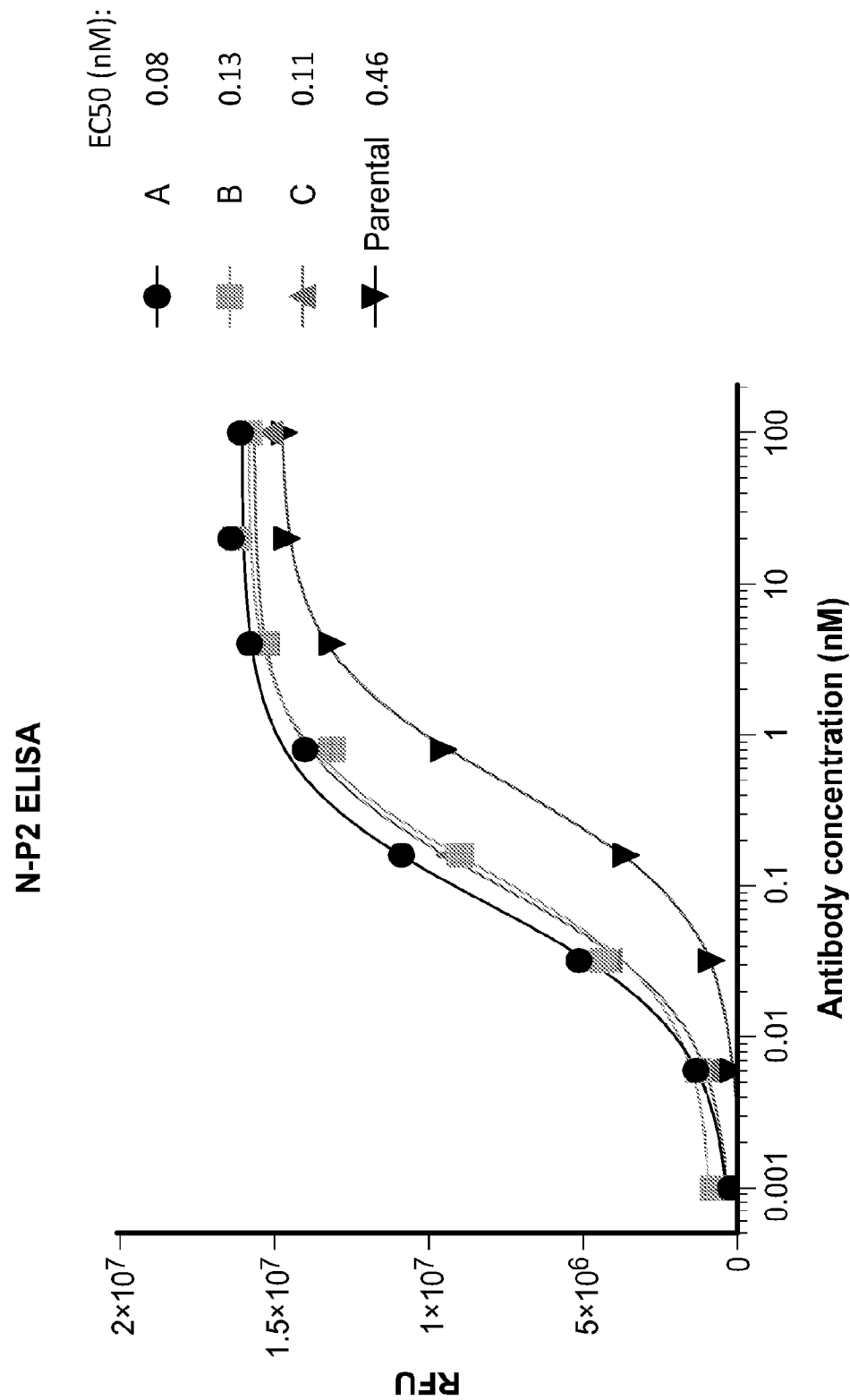


Figure 2A

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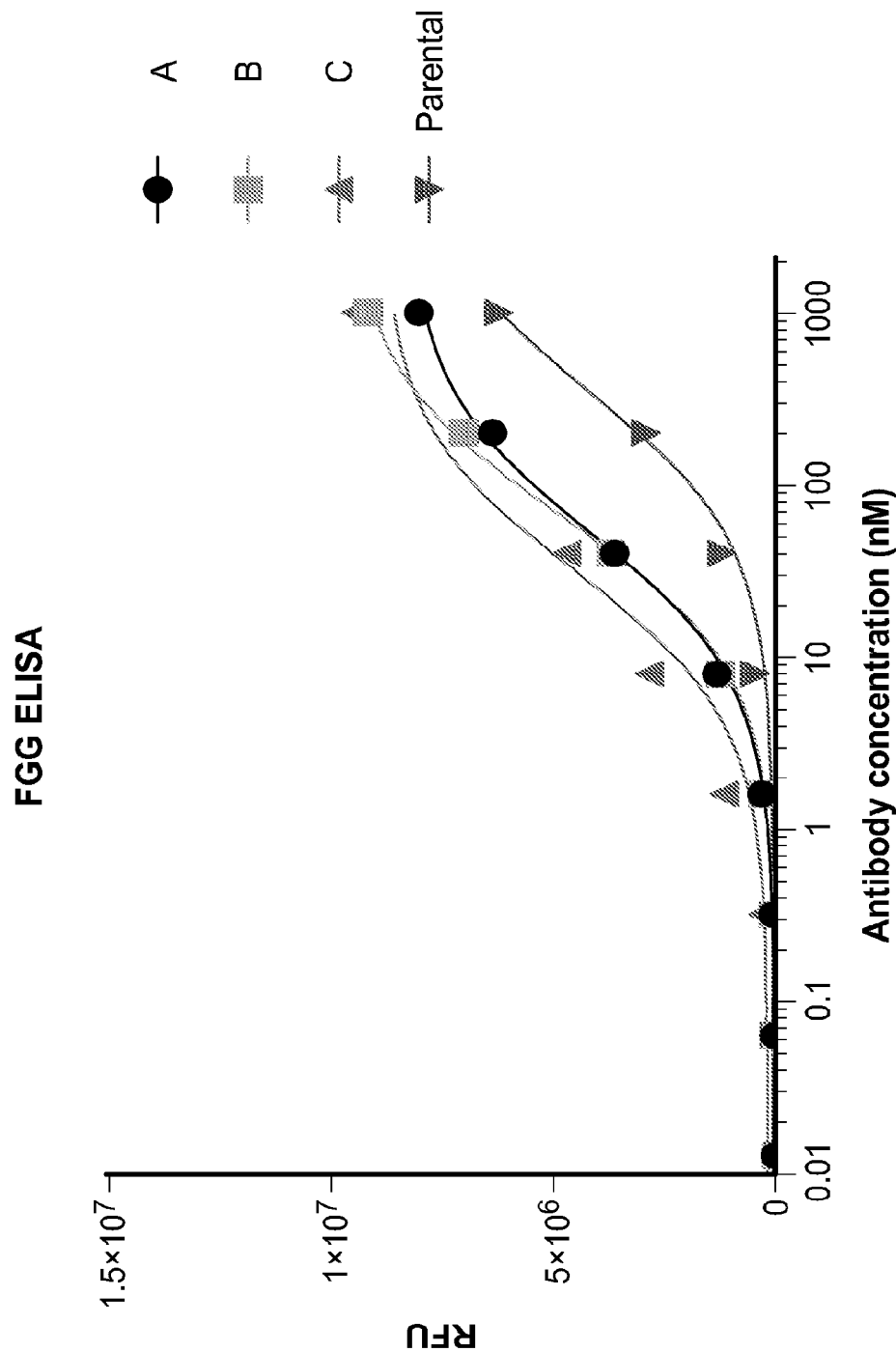


Figure 2B

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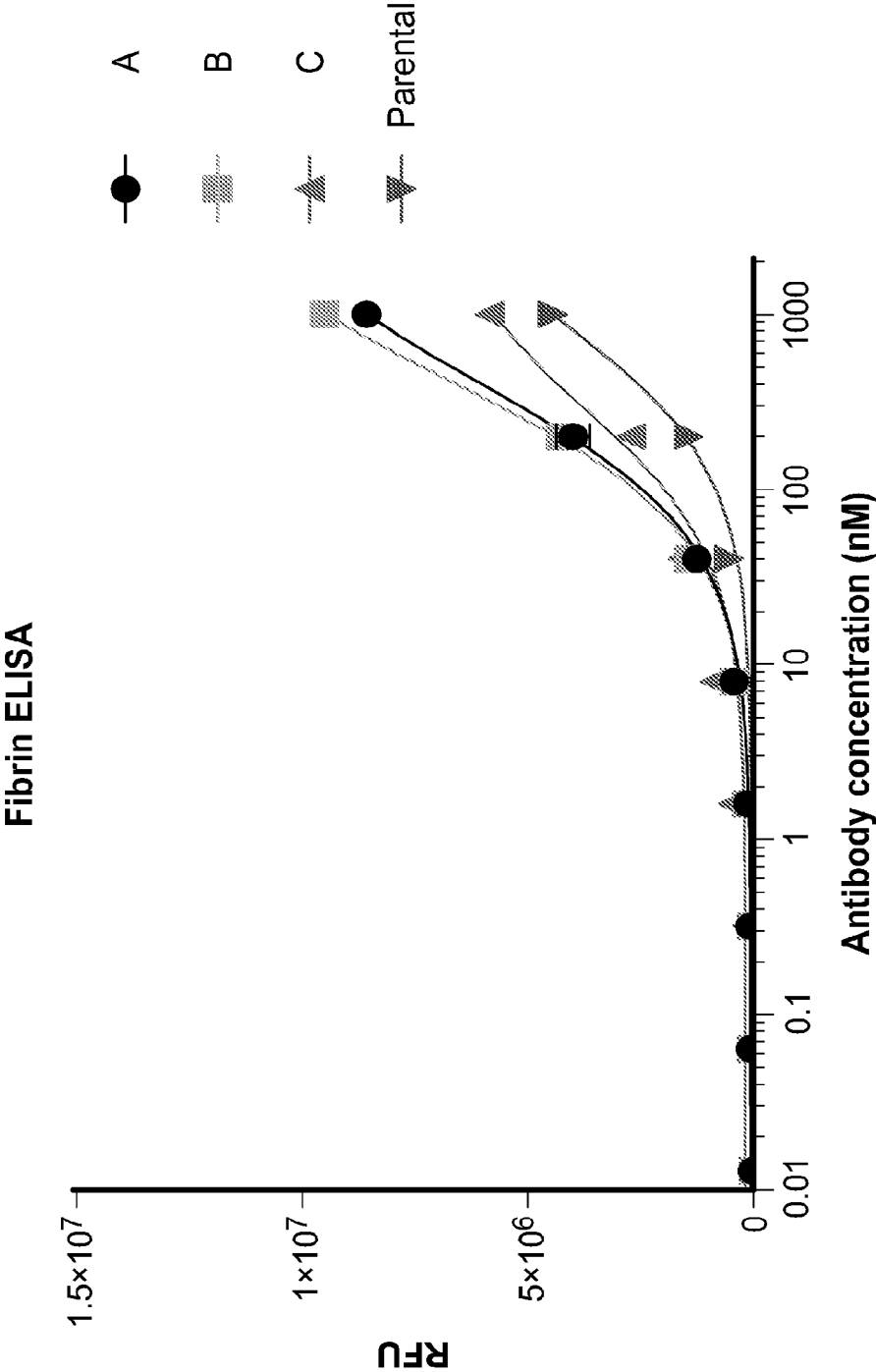
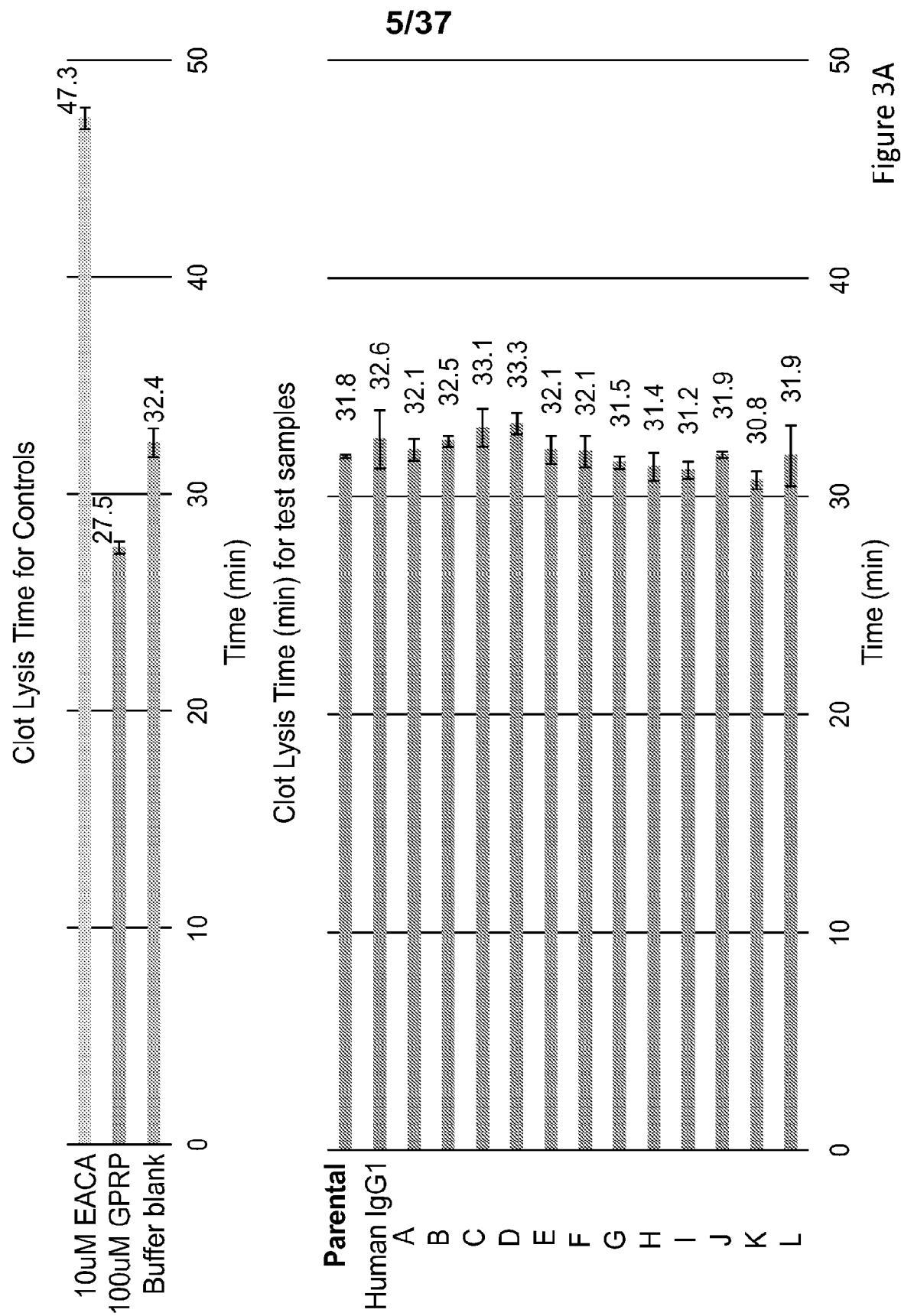


Figure 2C



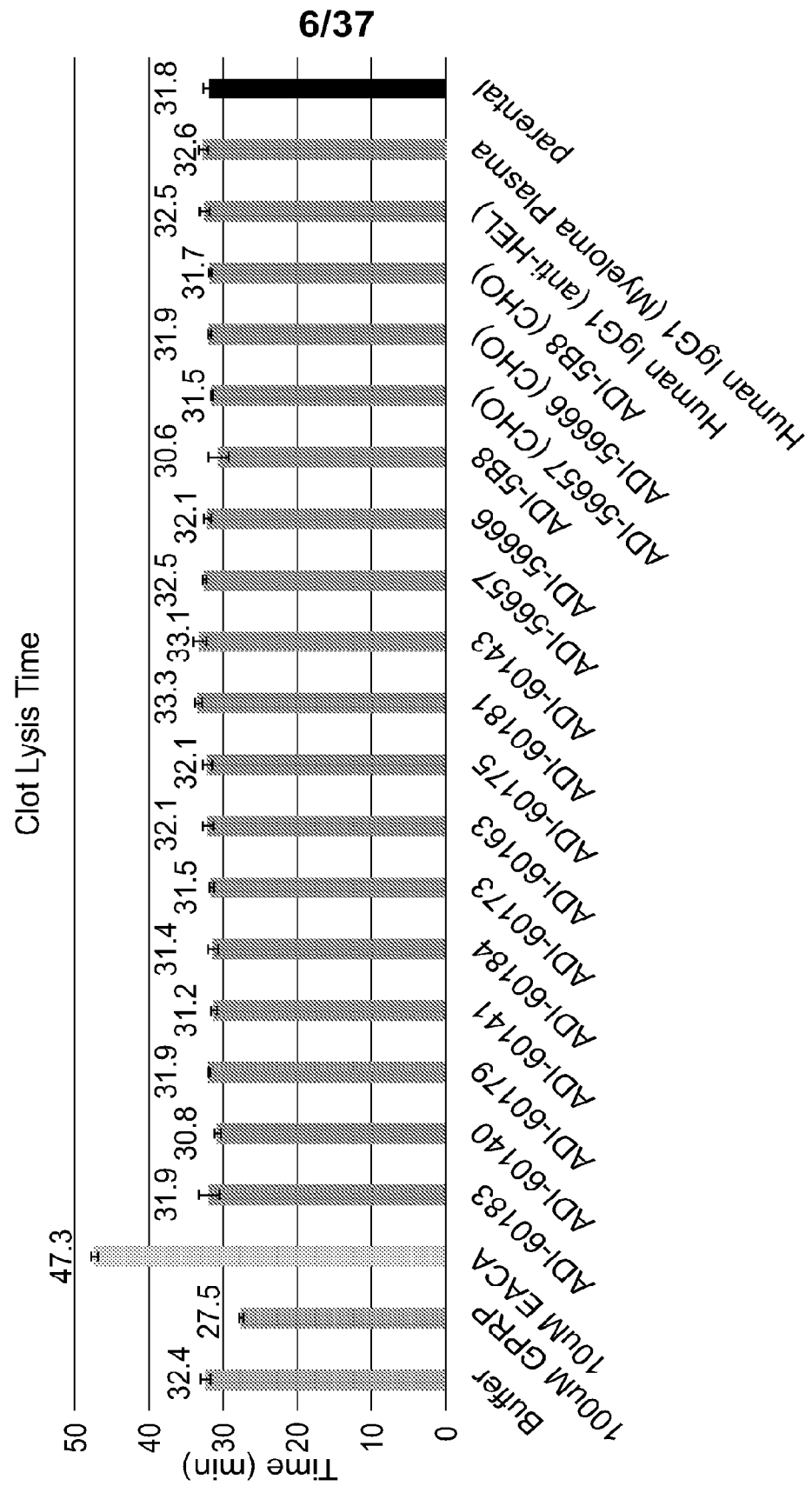


Figure 3B

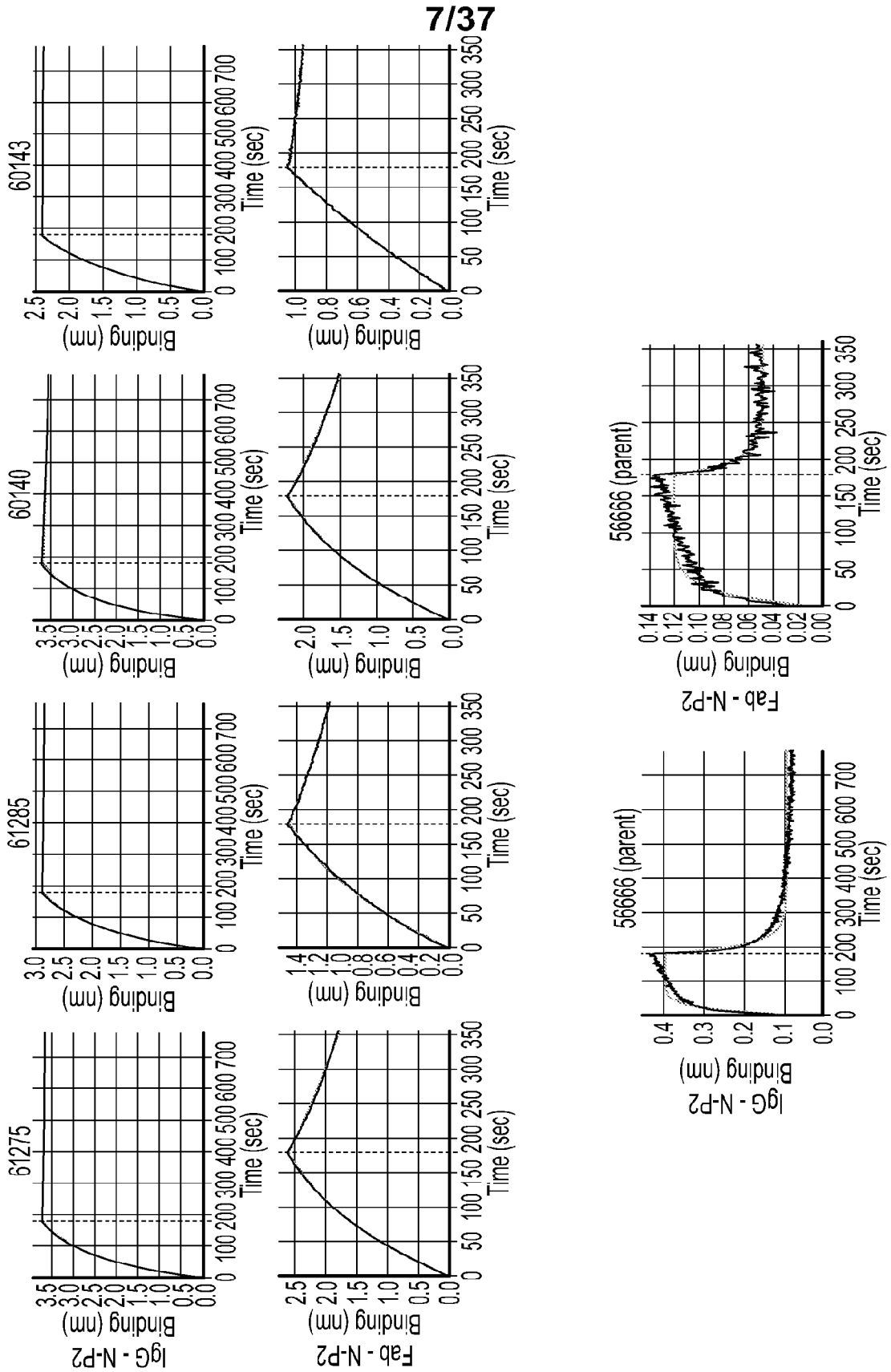
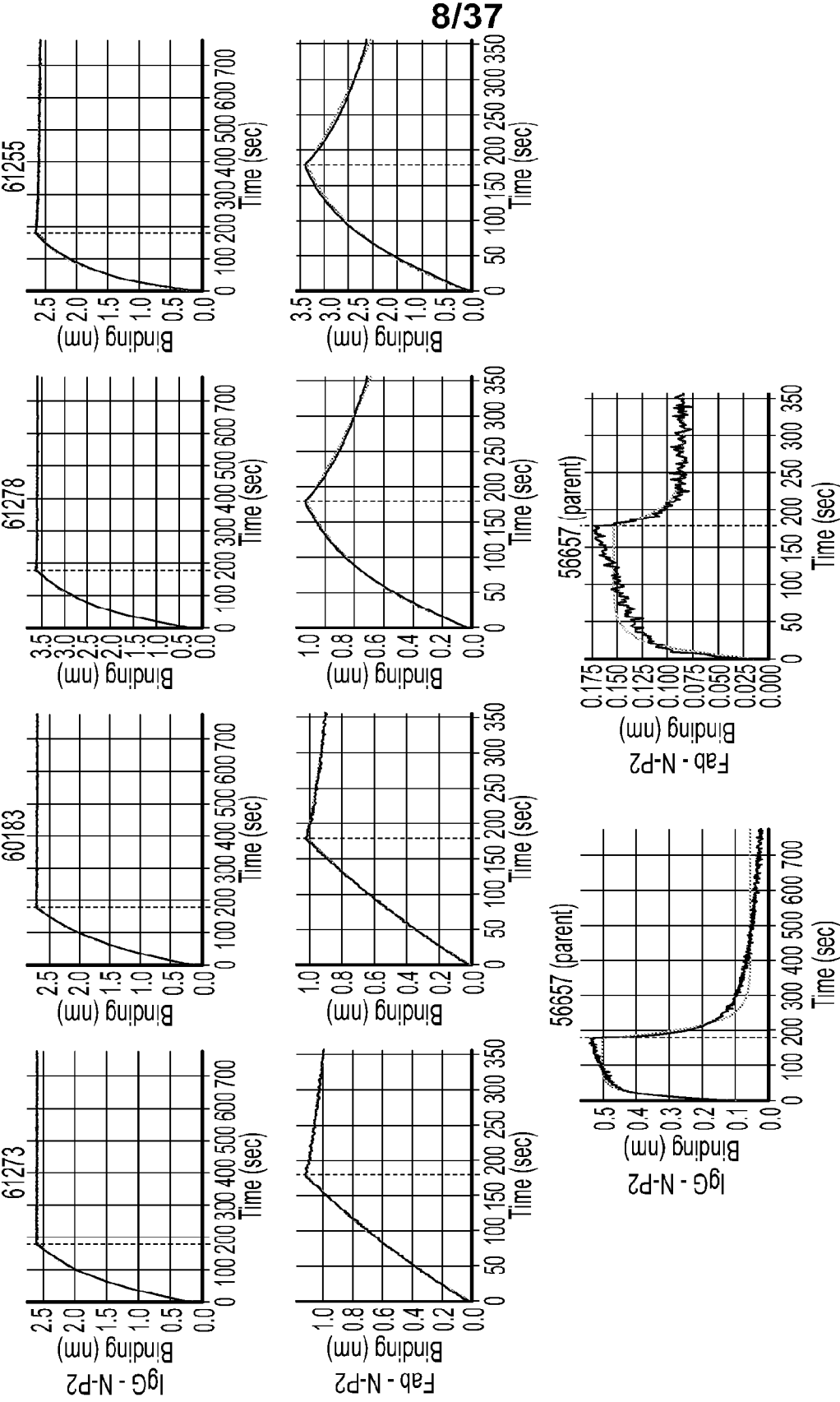


Figure 4A



N-term Biotinylated Fibrin P2G Peptide on SA tip:
IgG in solution (100 nM) [Avid]
Fab in solution (100 nM) [Monovalent]

Figure 4A (Cont.)

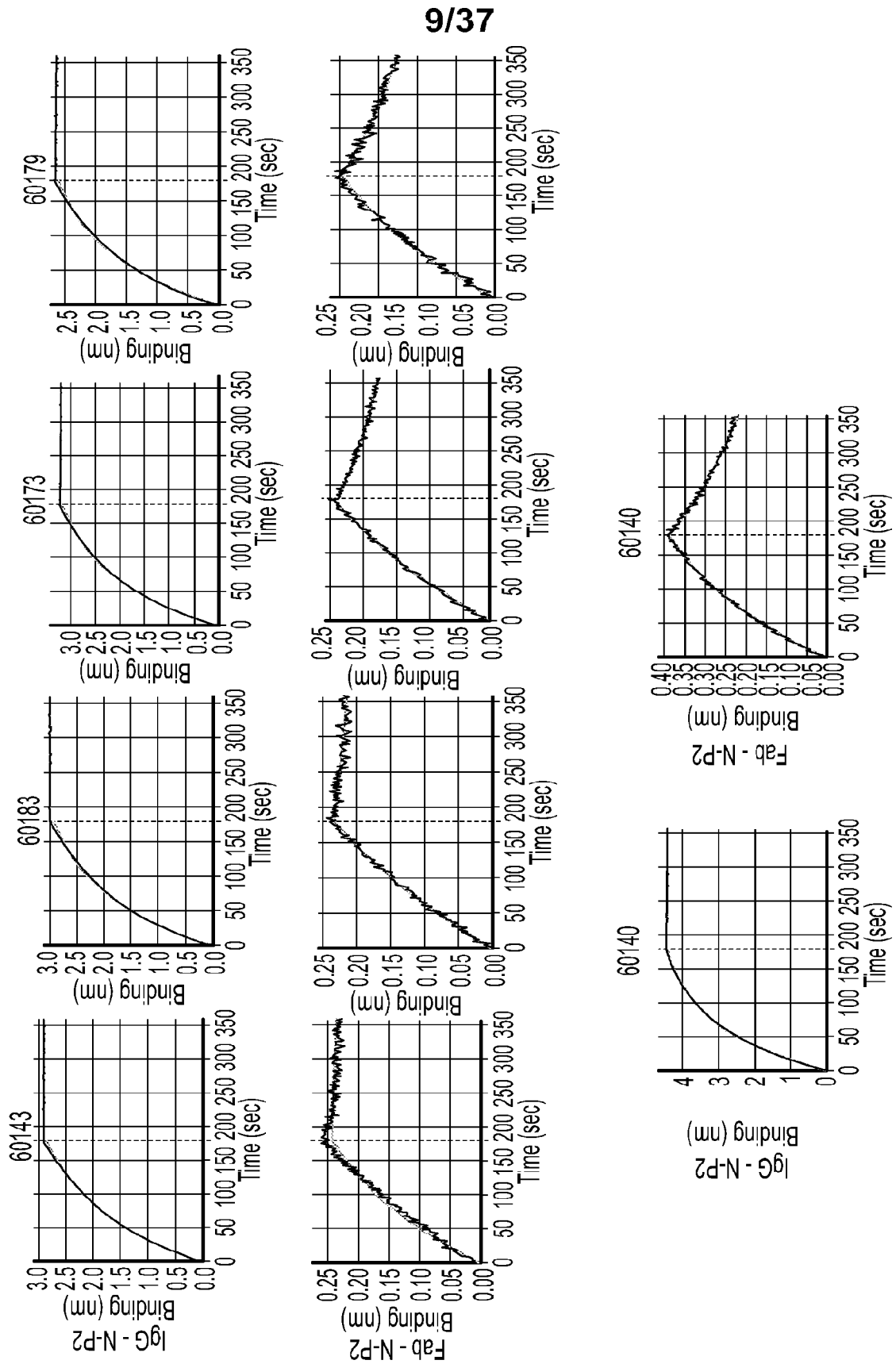


Figure 4B

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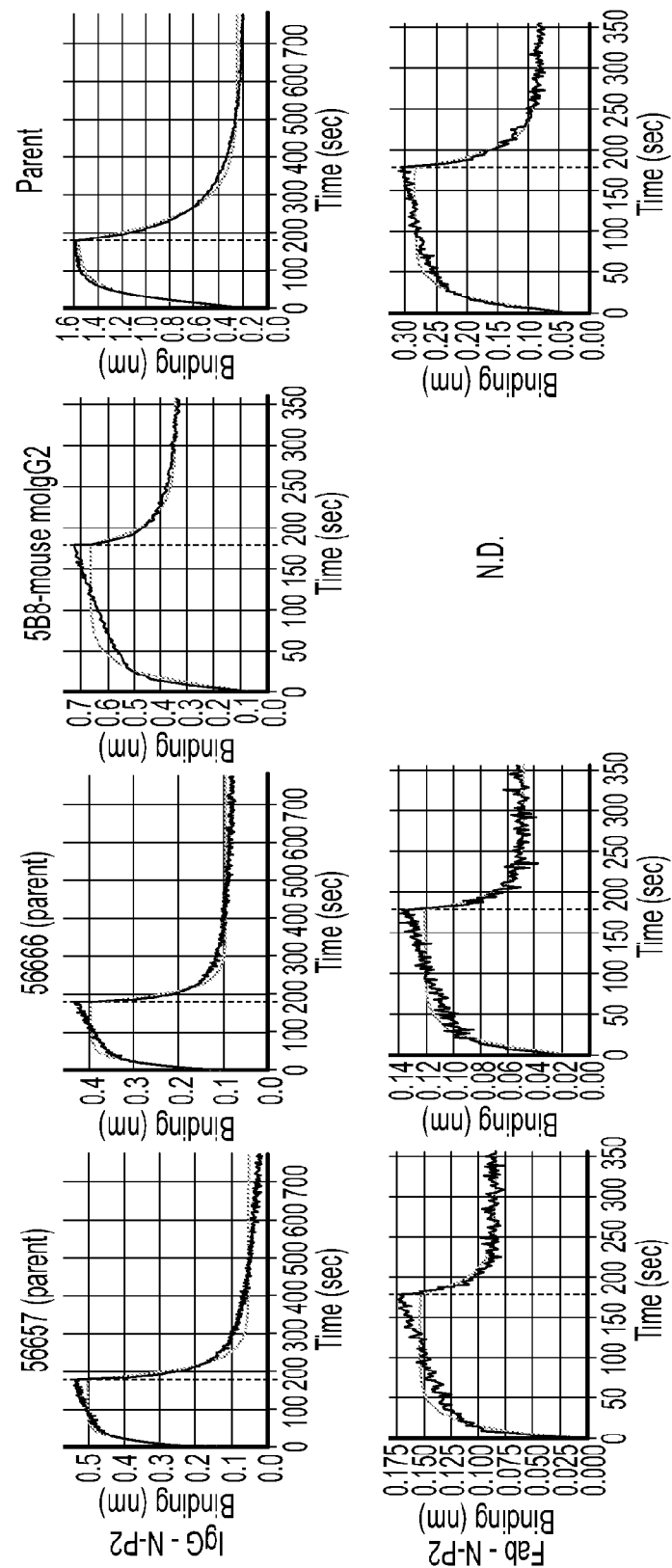


Figure 4B (Cont.)

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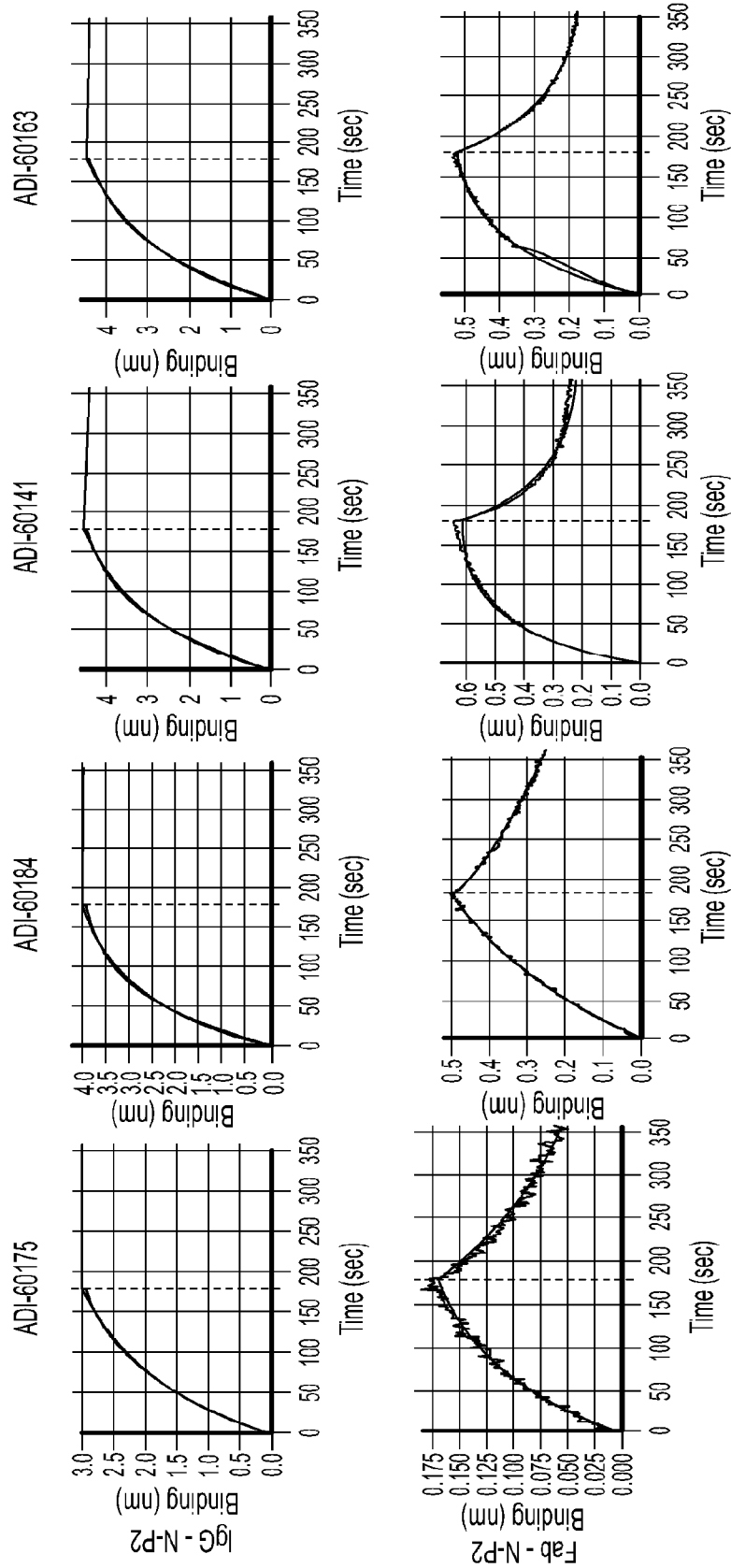


Figure 4C

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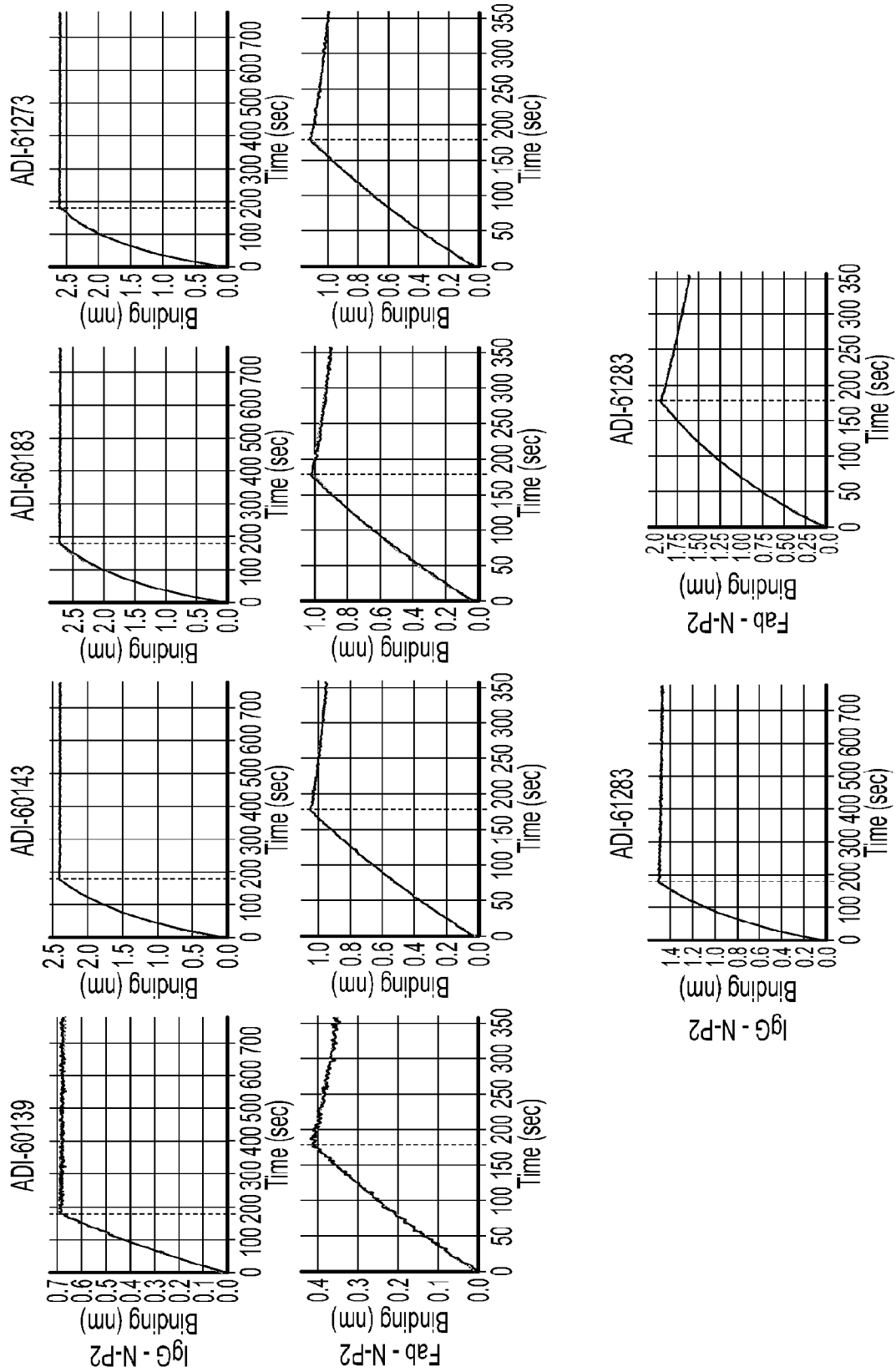


Figure 4D

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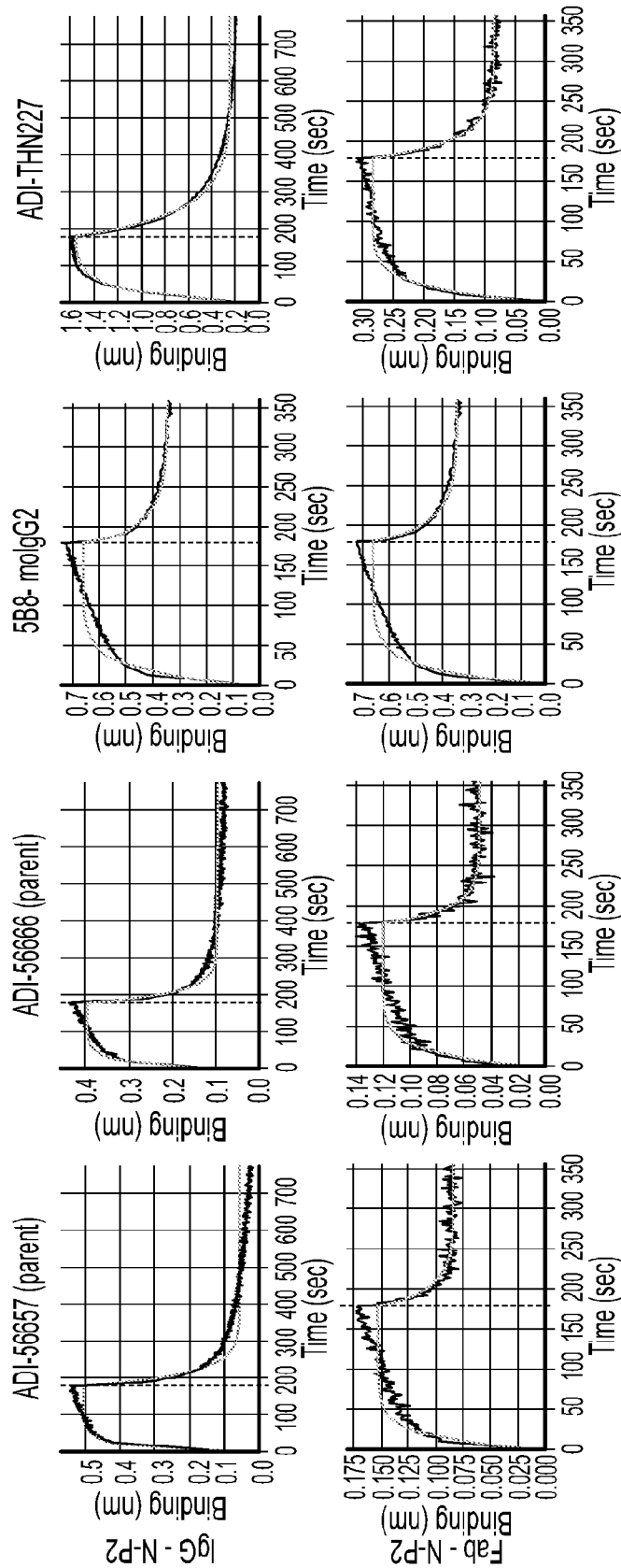


Figure 4D (Cont.)

Octet Fab binding to N-term Biotinylated P2 Gamma Peptide

N-term Biotinylated P2G peptide on SA sensor, 100nM Fab in solution
Normalized y-axis

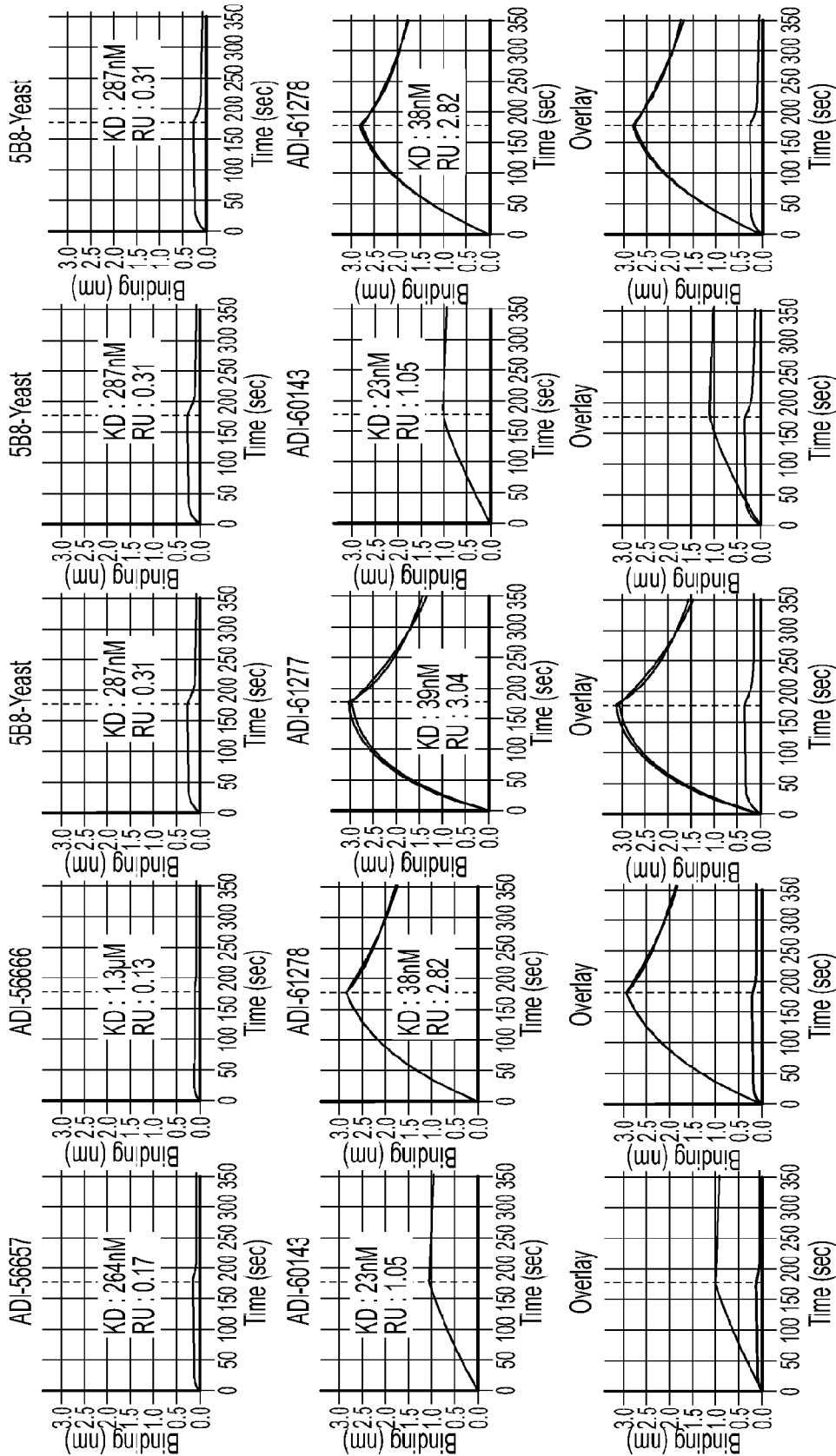
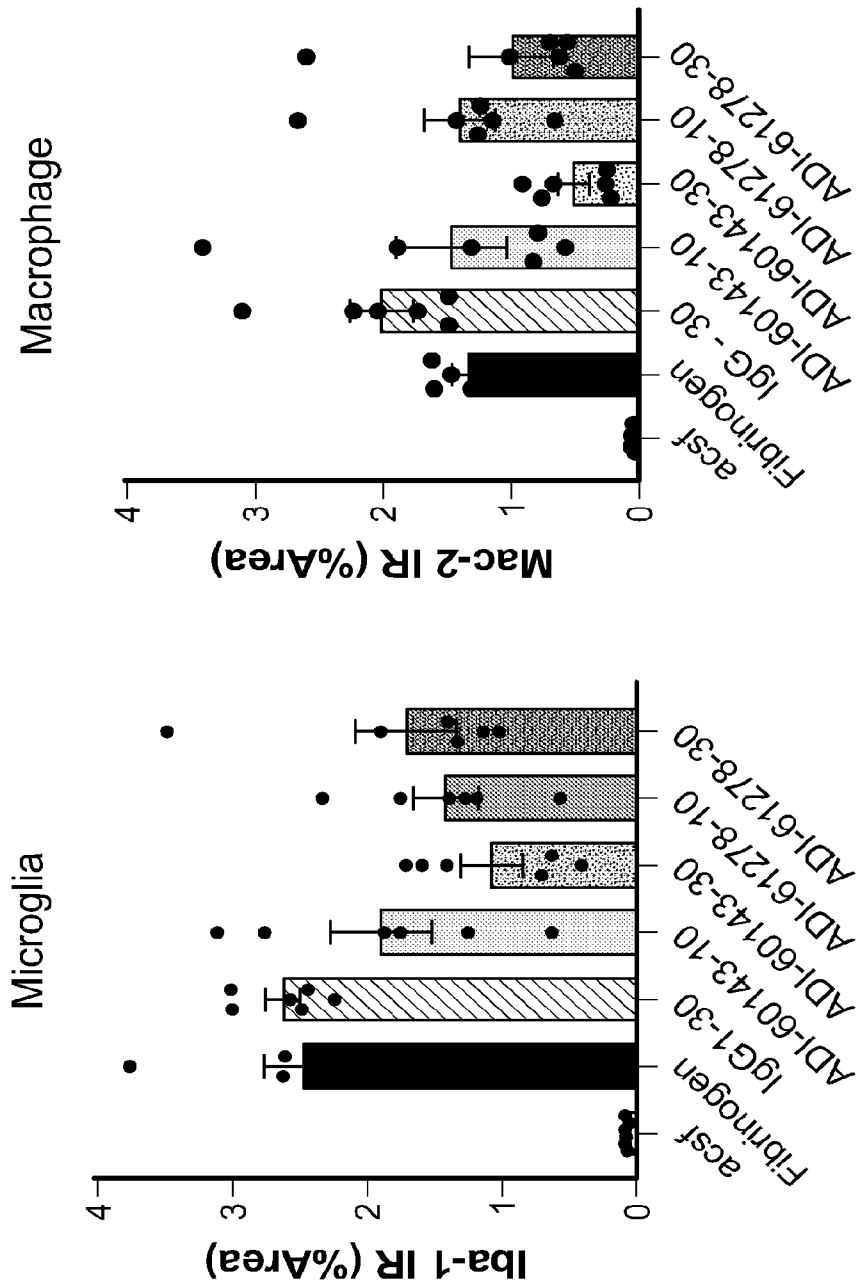


Figure 5

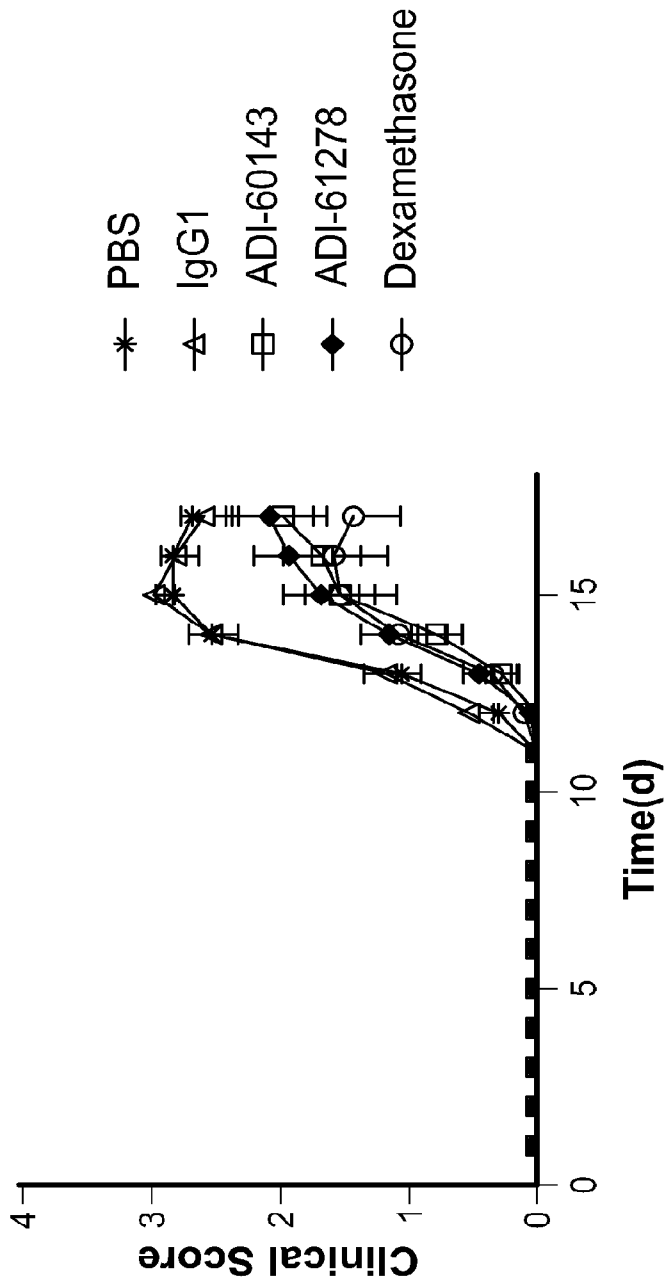
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10 = 10 mg/kg
30 = 30 mg/kg

Figure 6

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Prophylactic injection of antibodies starting at day 0 (5 mg/kg i.p. every 3 days)

Figure 7

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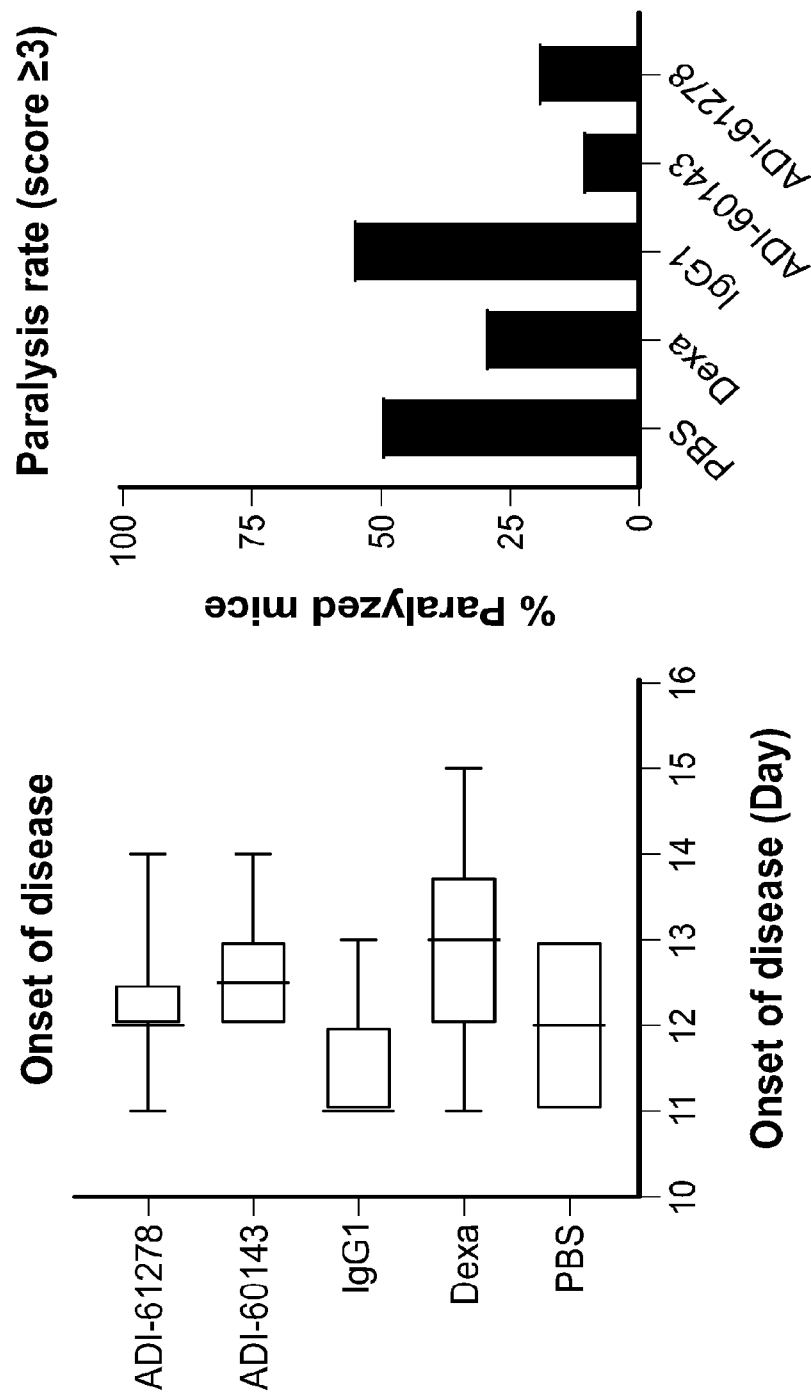


Figure 8

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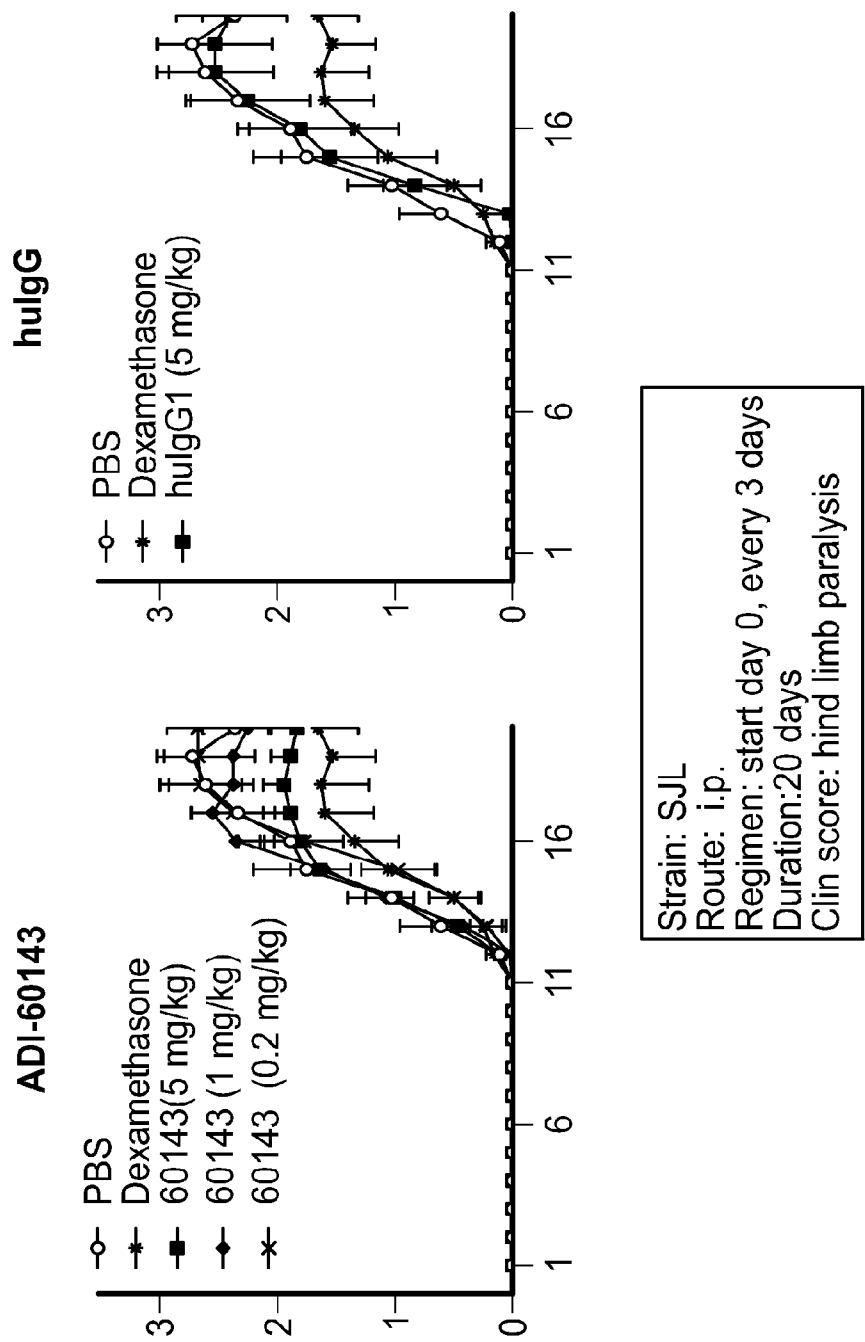


Figure 9

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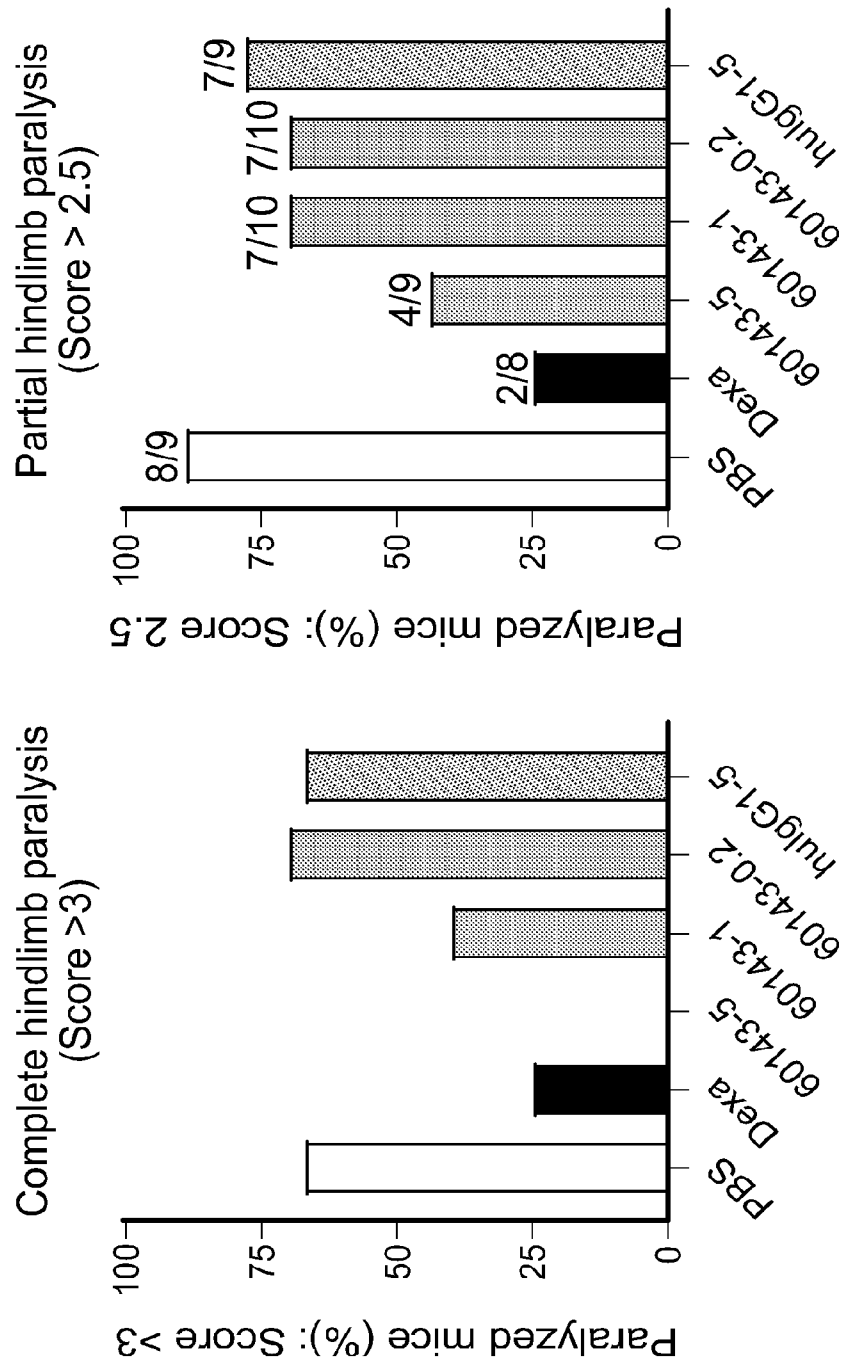


Figure 10

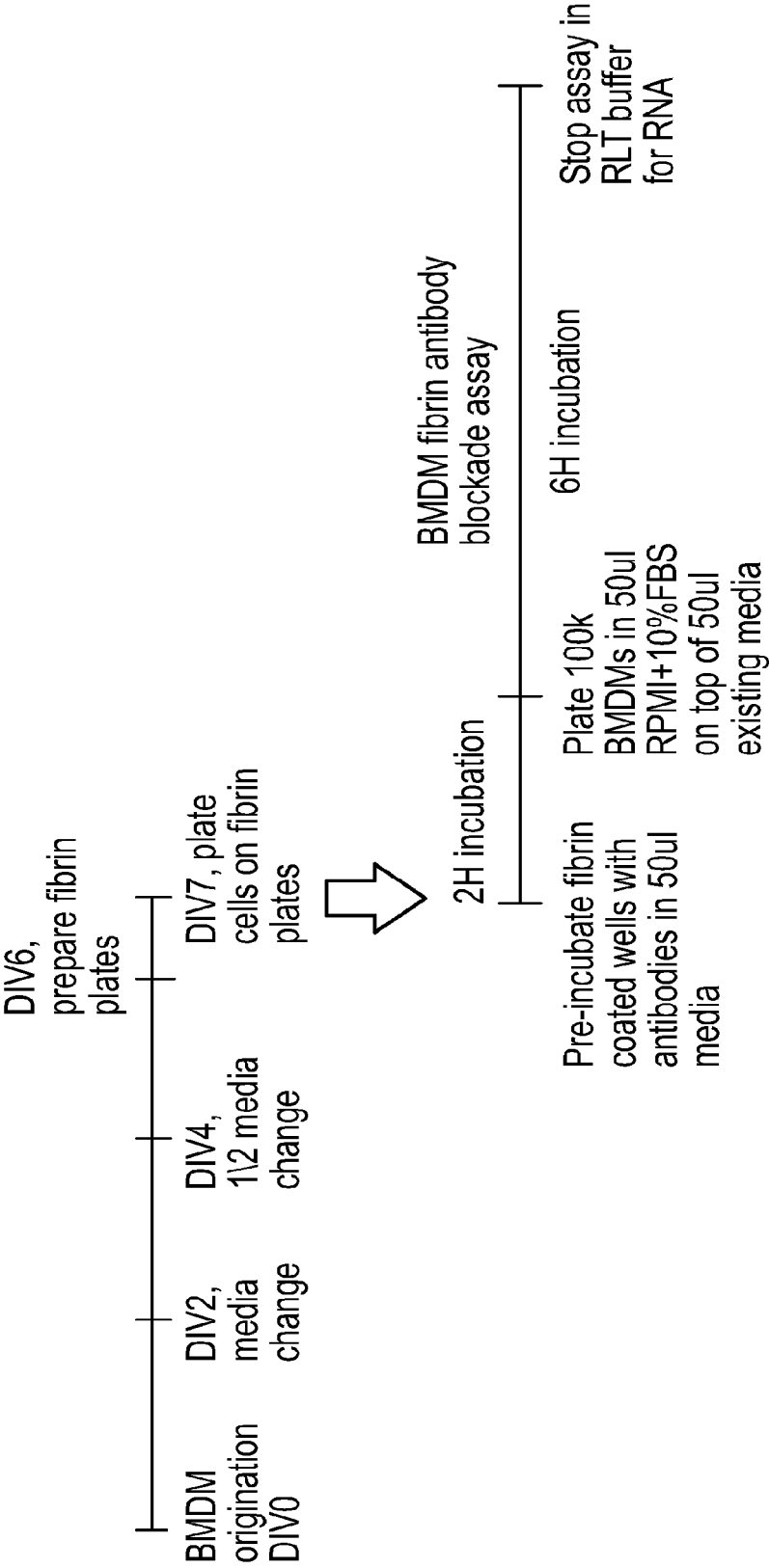


Figure 11

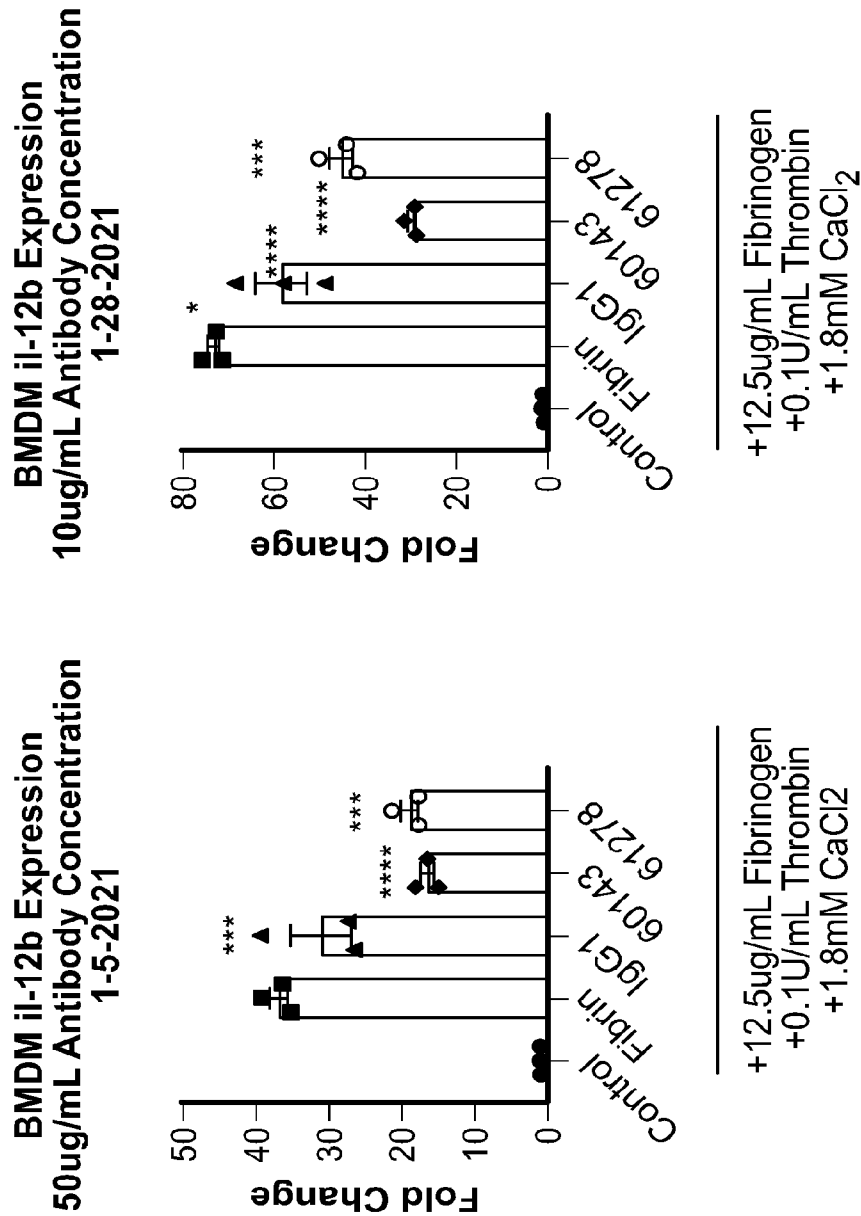
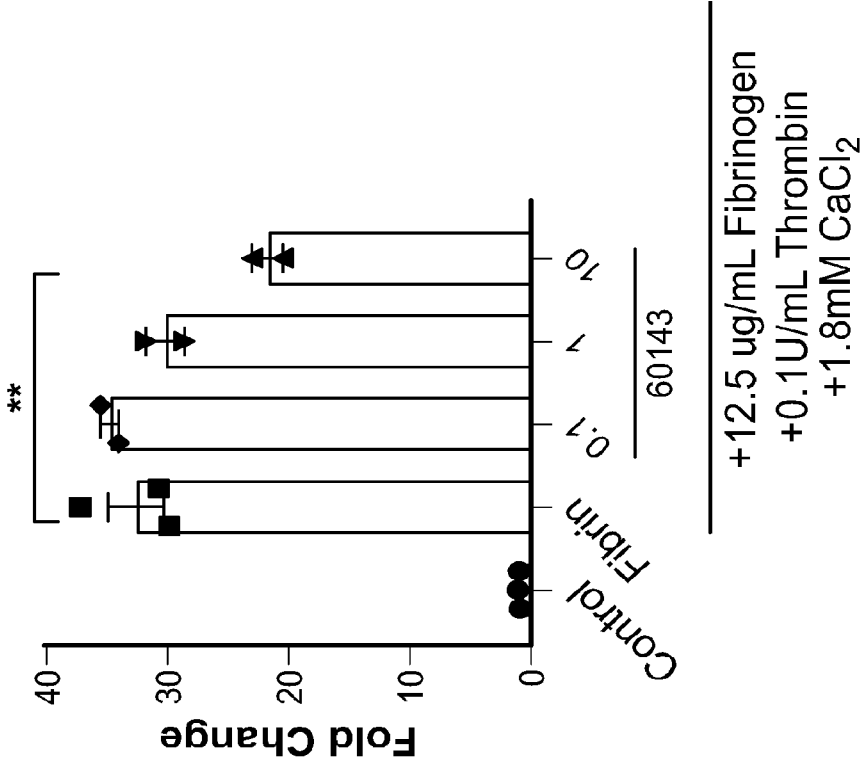


Figure 12

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**BMDM il-12b Expression
ADI-60143 Dose Titration
3-1-2021**



**BMDM il-12b Expression
61278 Dose Response
2-9-2021**

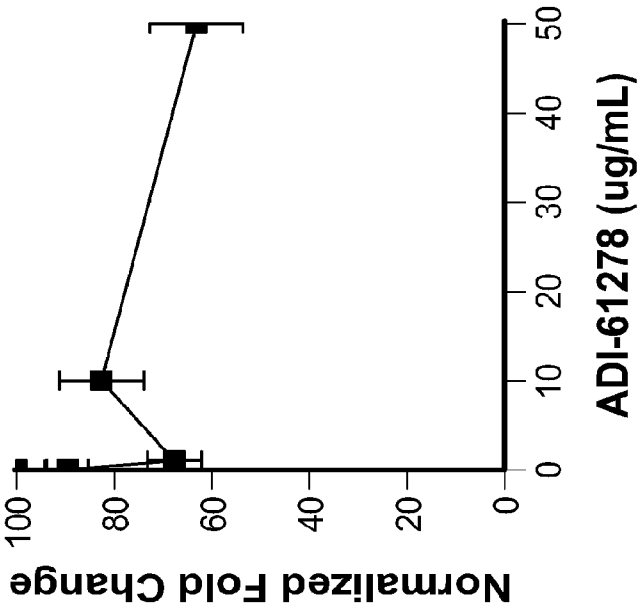


Figure 13

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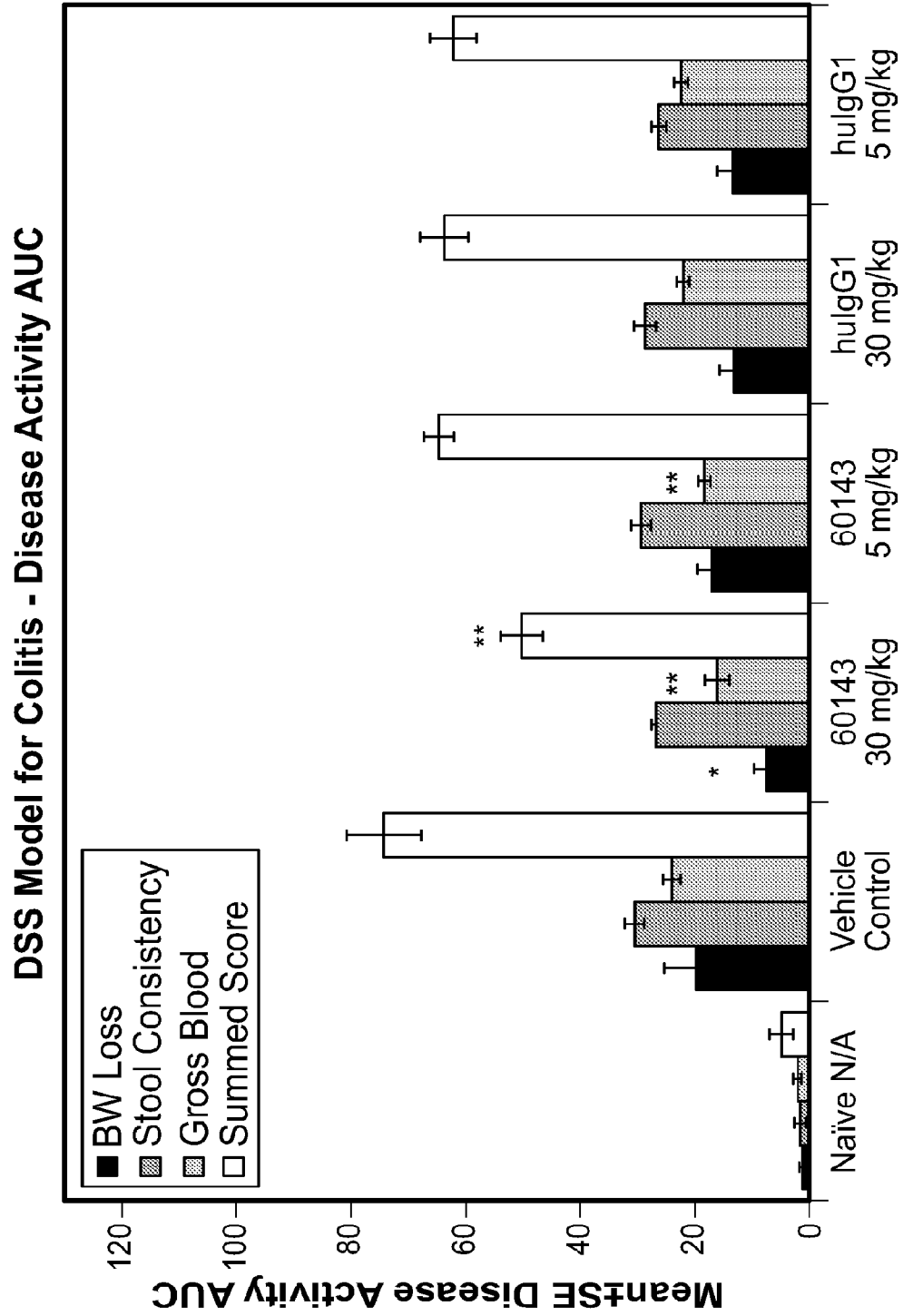


Figure 14

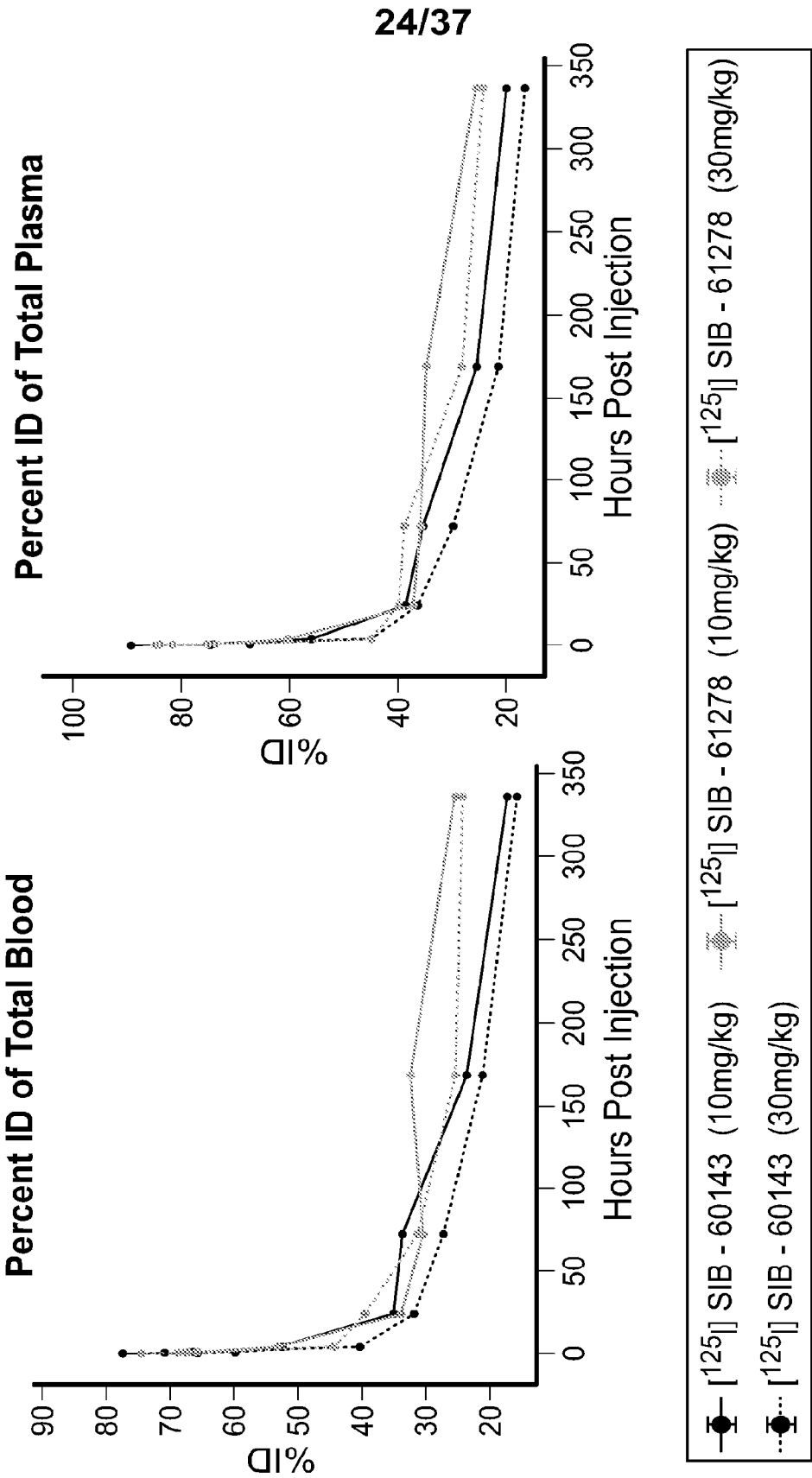


Figure 15B

Figure 15A

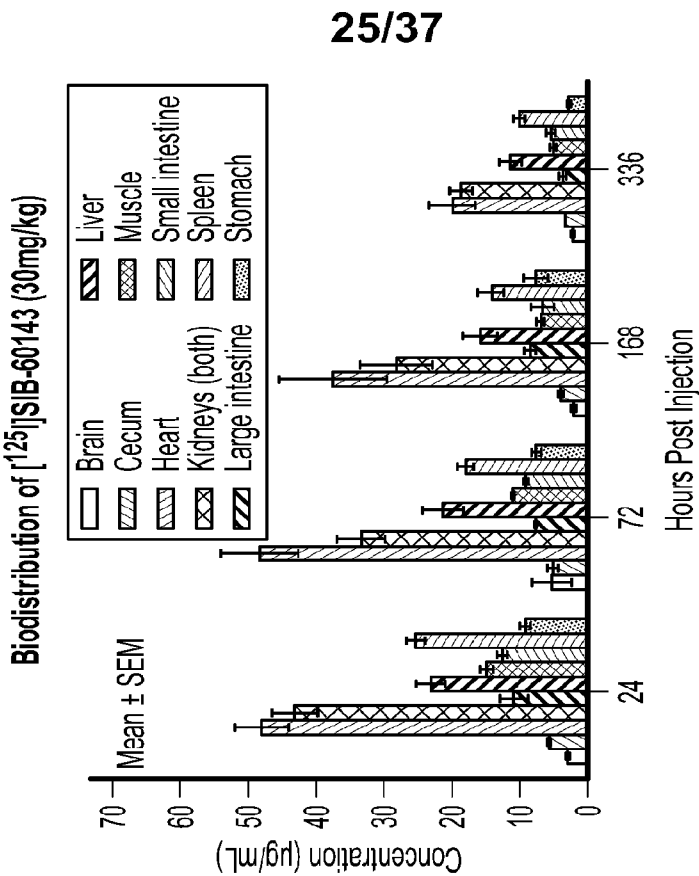


Figure 16B

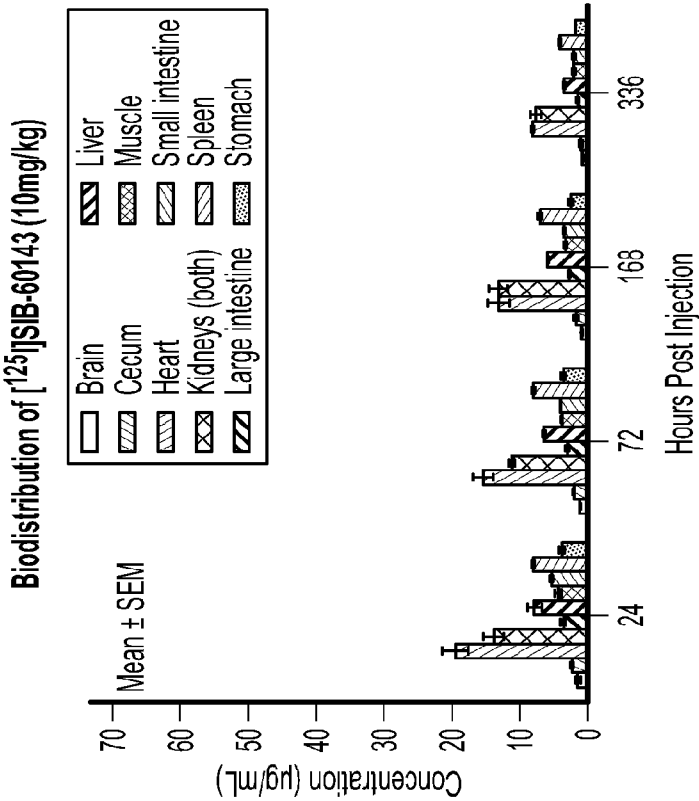


Figure 16A

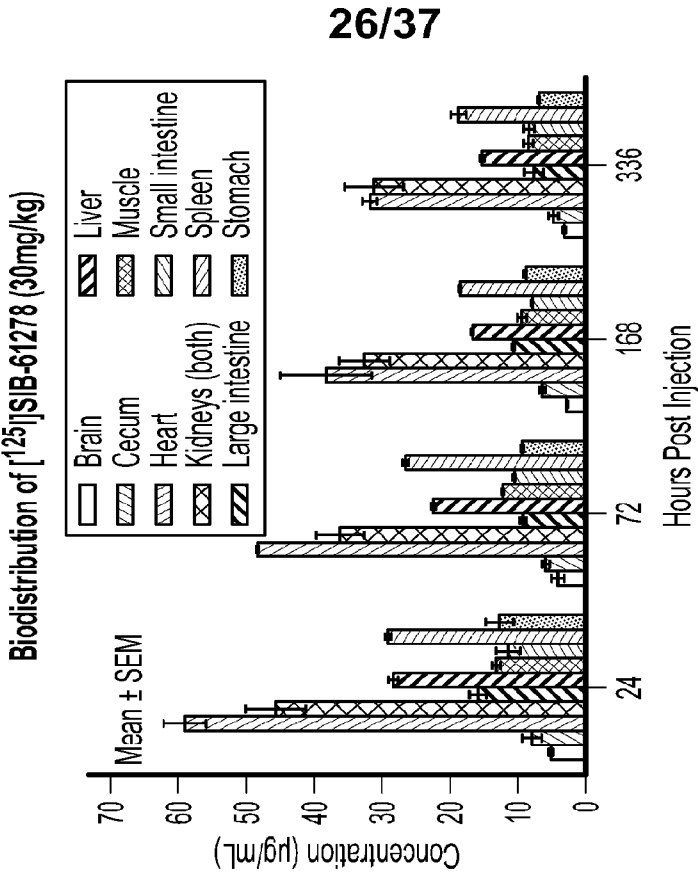


Figure 16D

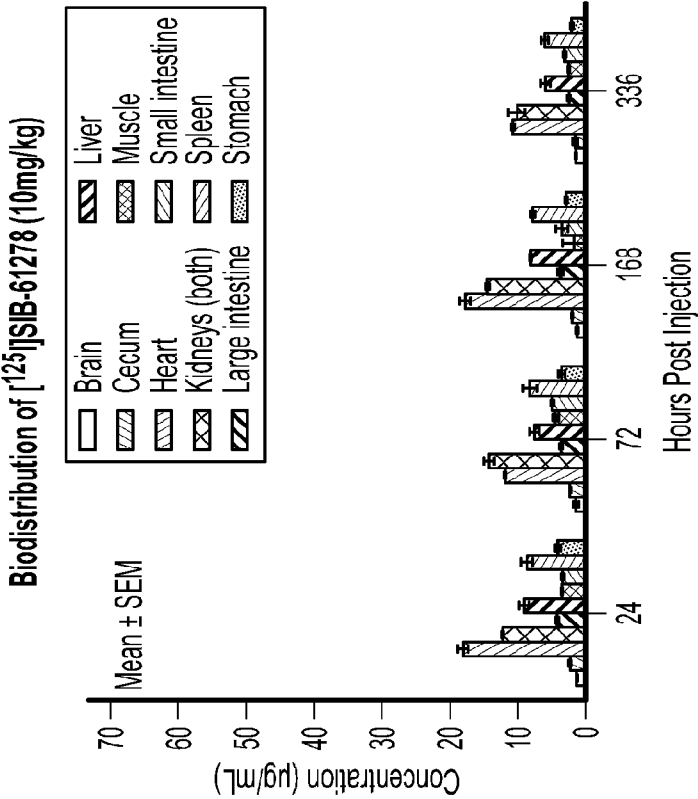


Figure 16C

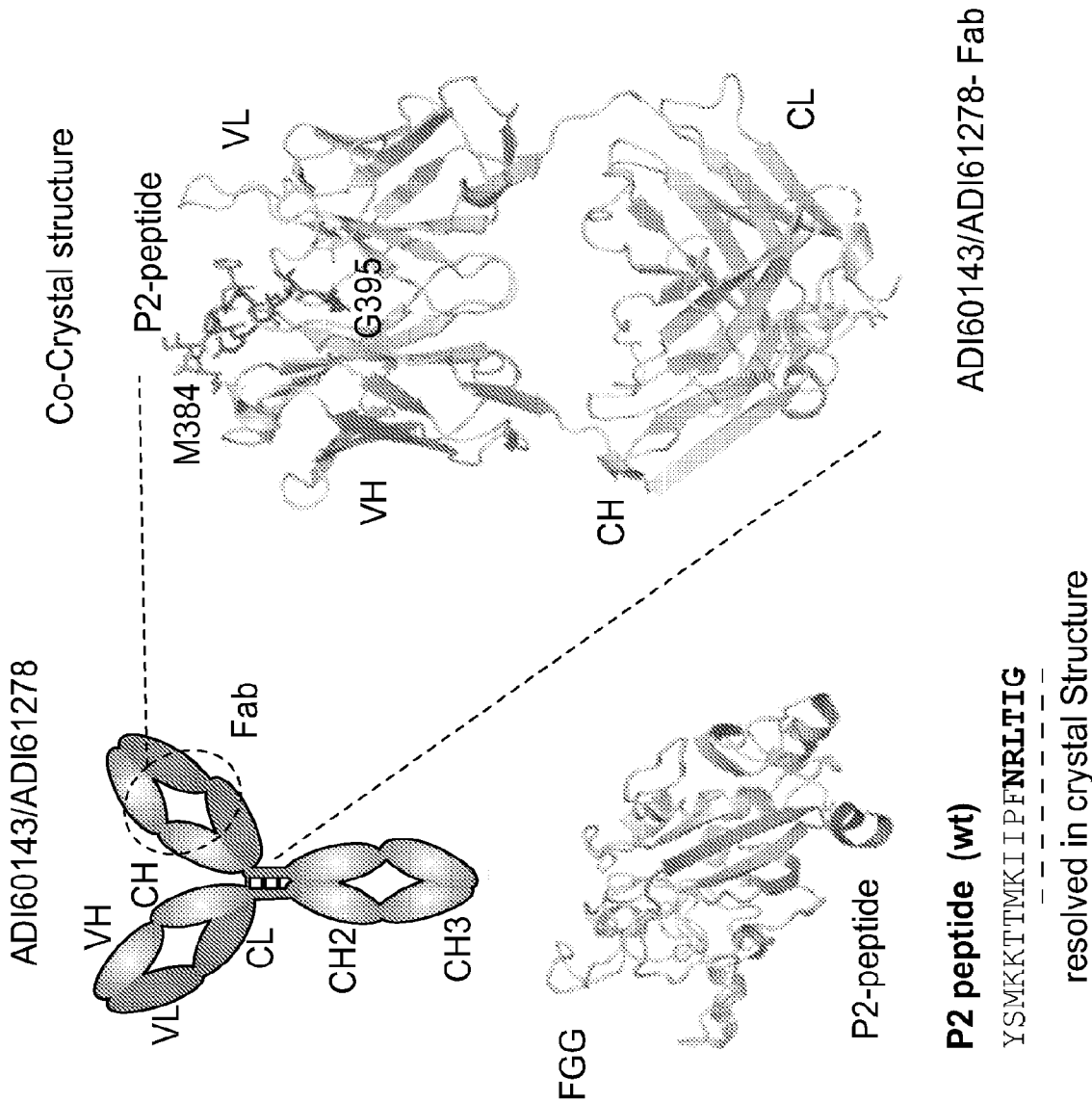
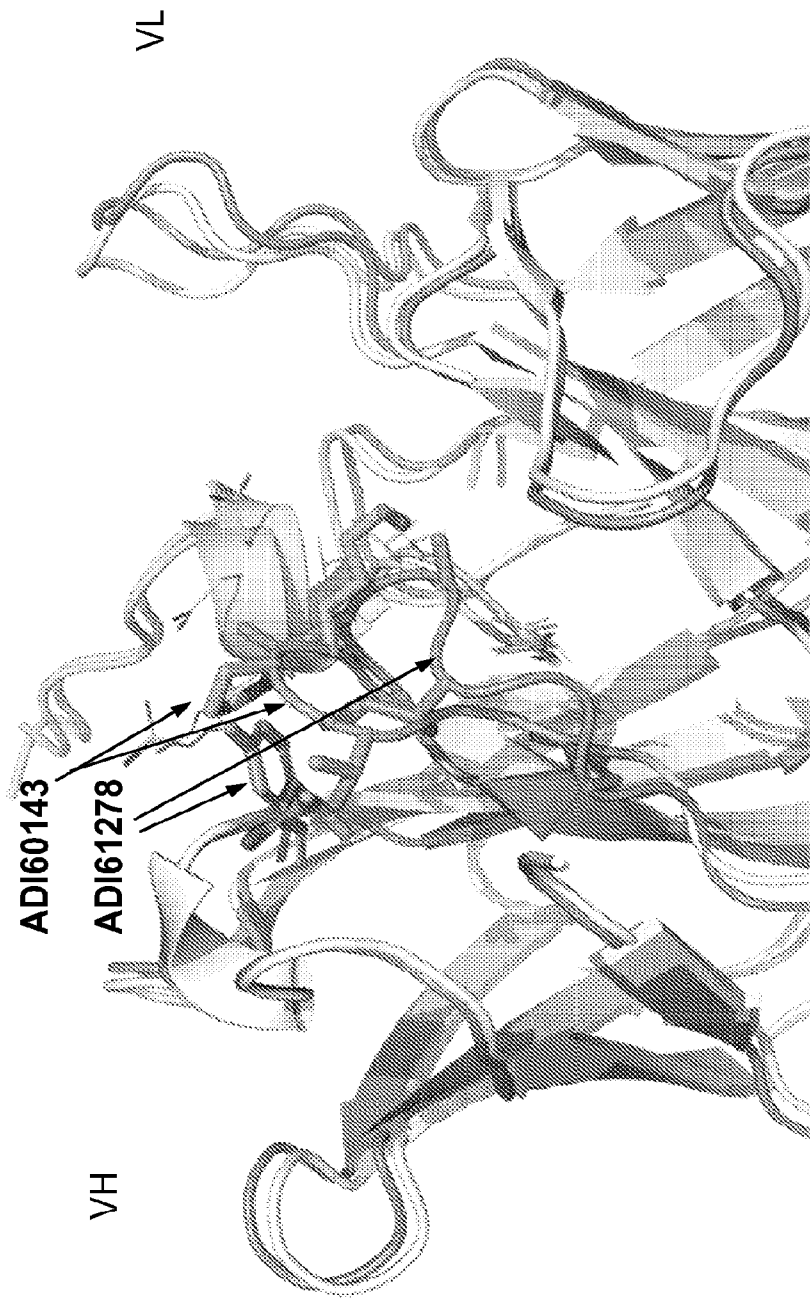


Figure 17



Name	Type	CDR1	CDR2	CDR3
ADI60143 HC	VH	<u>STW</u> IH	LIDPSDSYTNYNQKFRG	<u>SKPT</u> GG
ADI61278 HC	VH	<u>SYW</u> IH	LIDPSDSYTNYNQKFRG	<u>SDAT</u> GG

Figure 18

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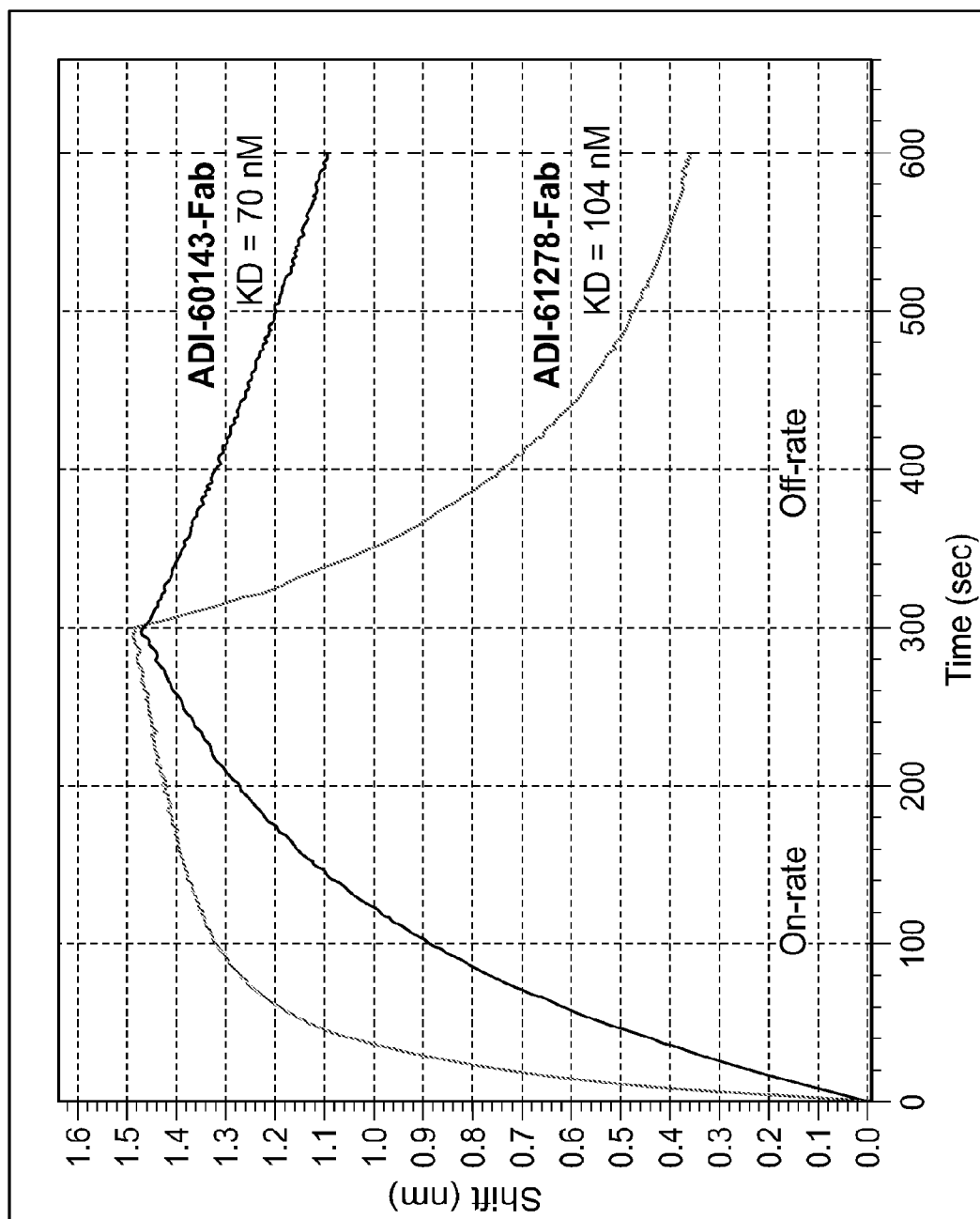


Figure 19

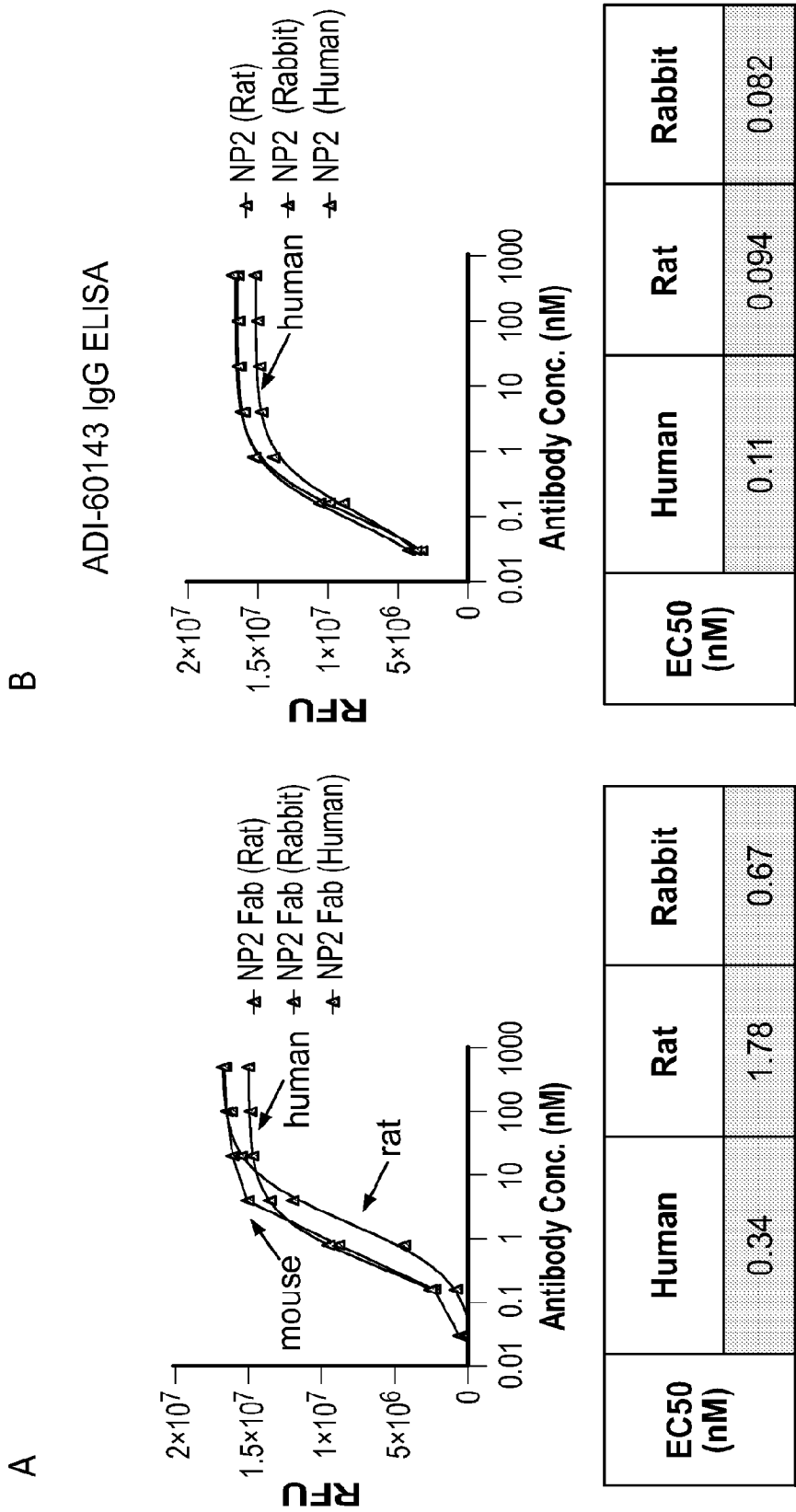
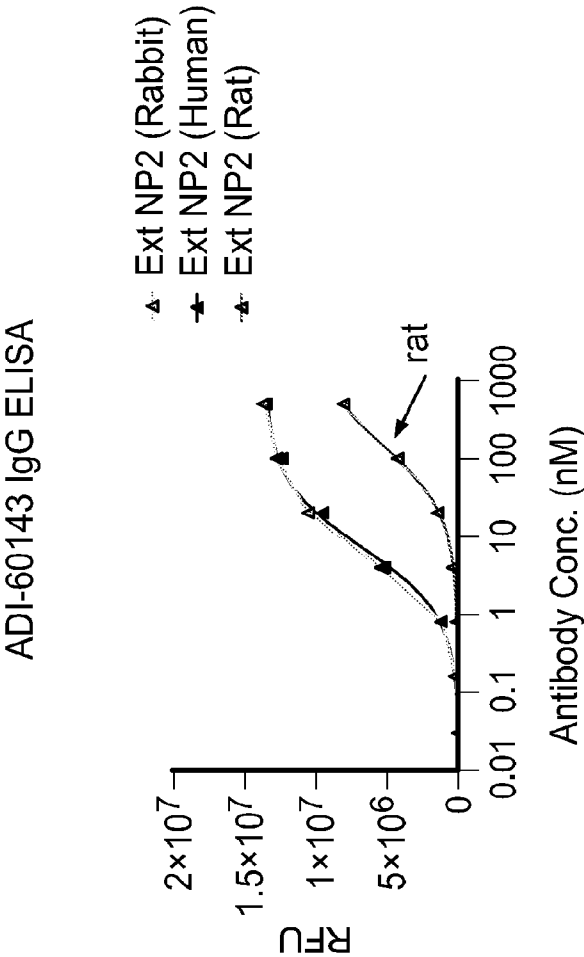


Figure 20



EC50 (nM)	Human	Rat	Rabbit
	7.248	139.2	5.972

Figure 21

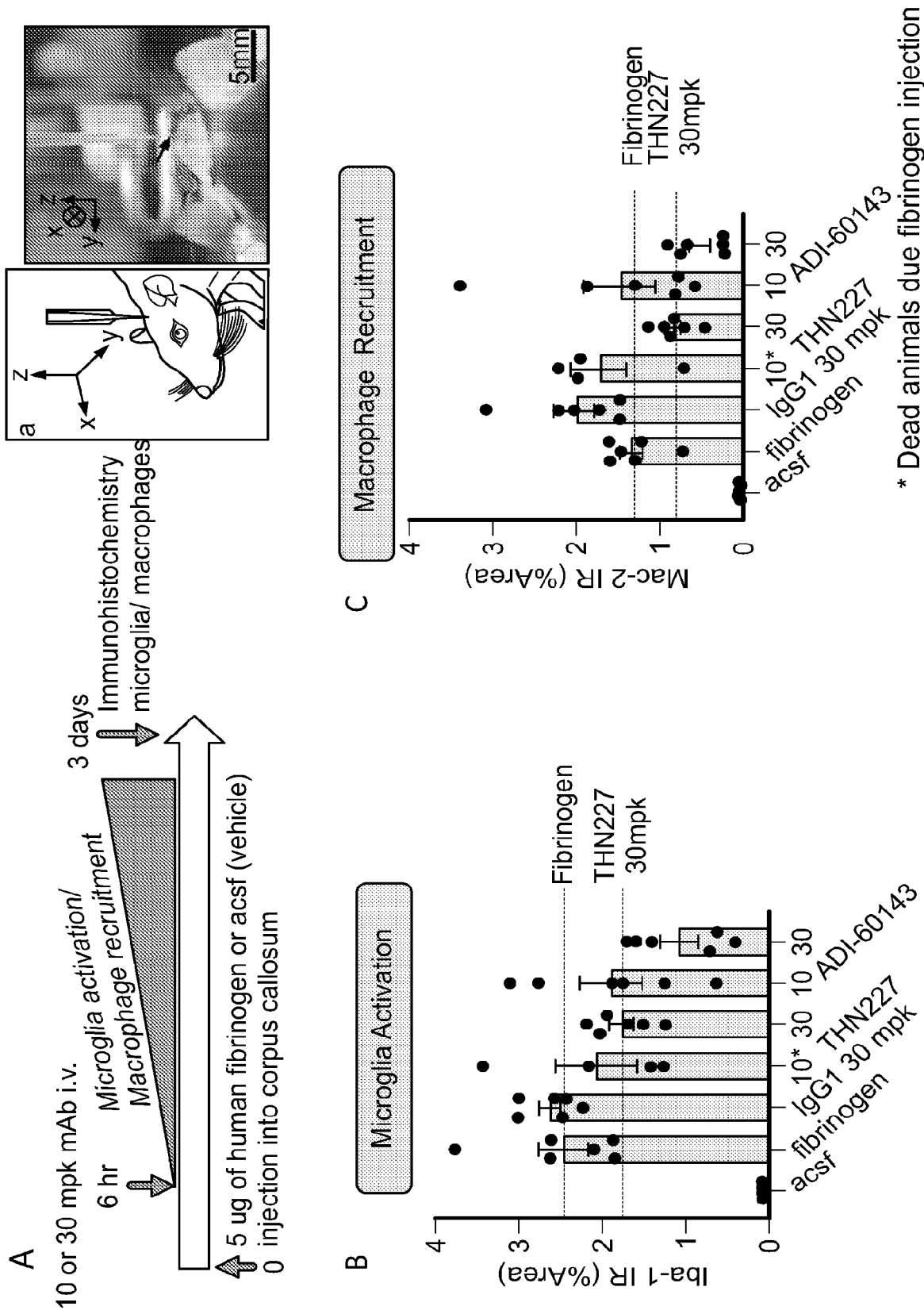
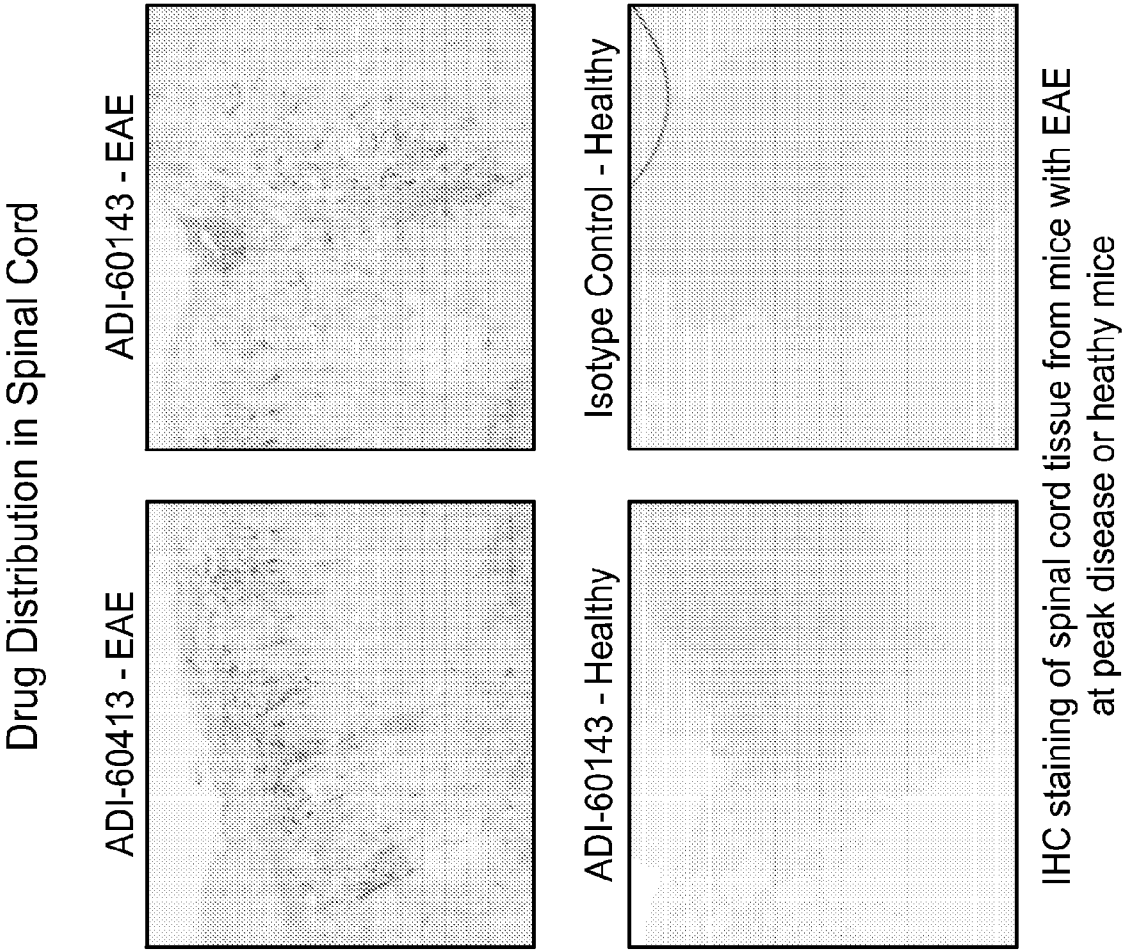


Figure 22



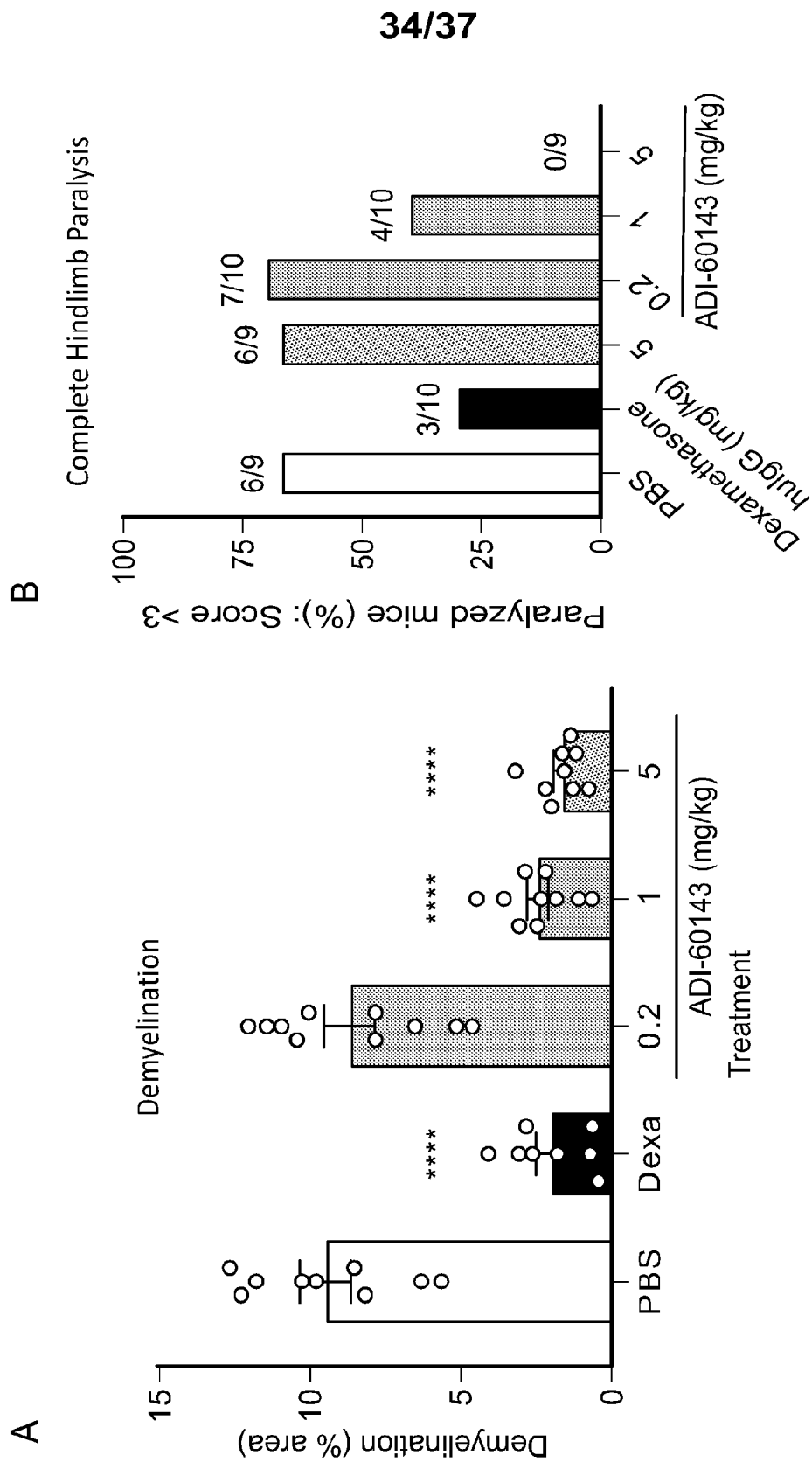


Figure 24

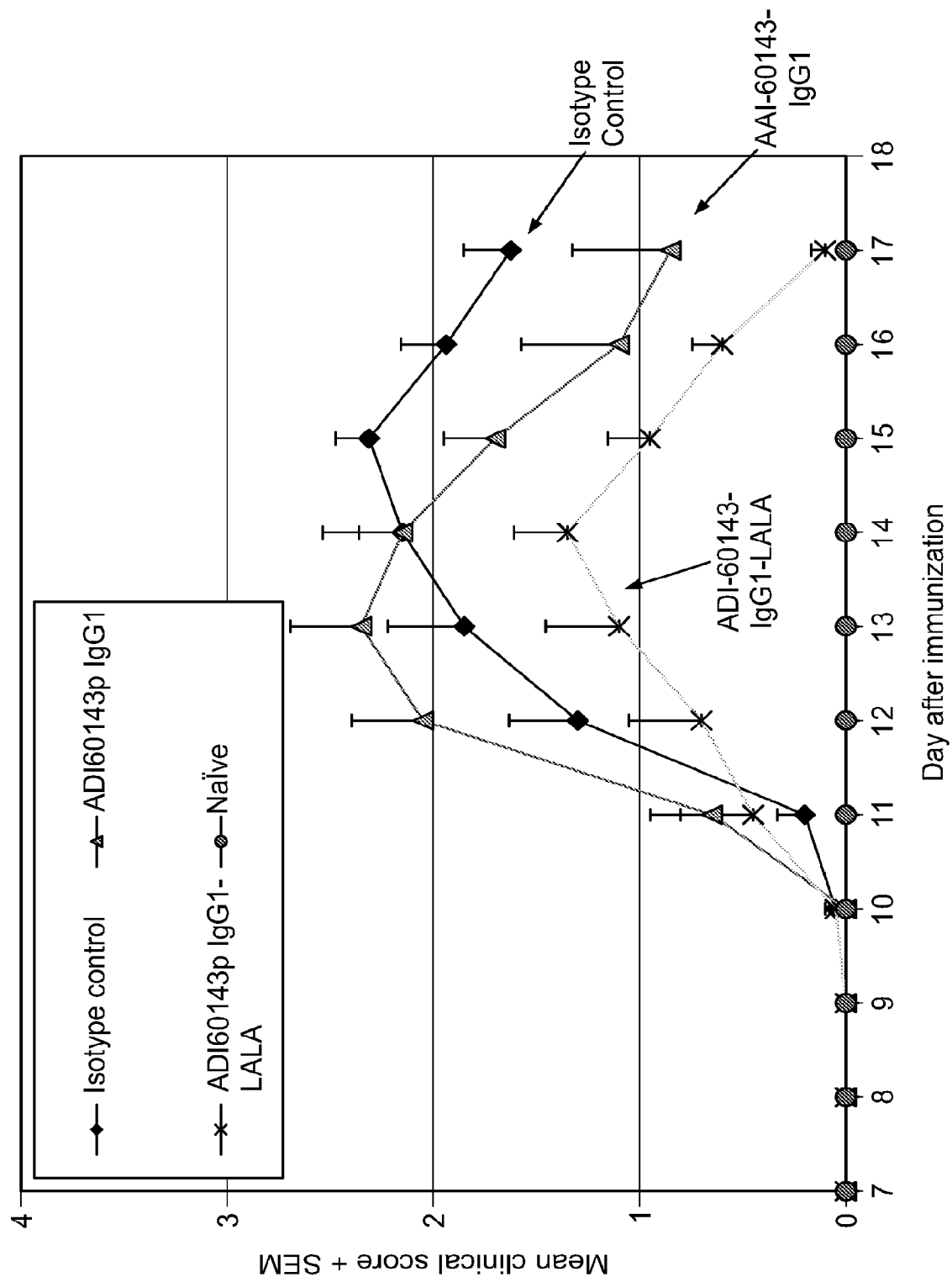


Figure 25

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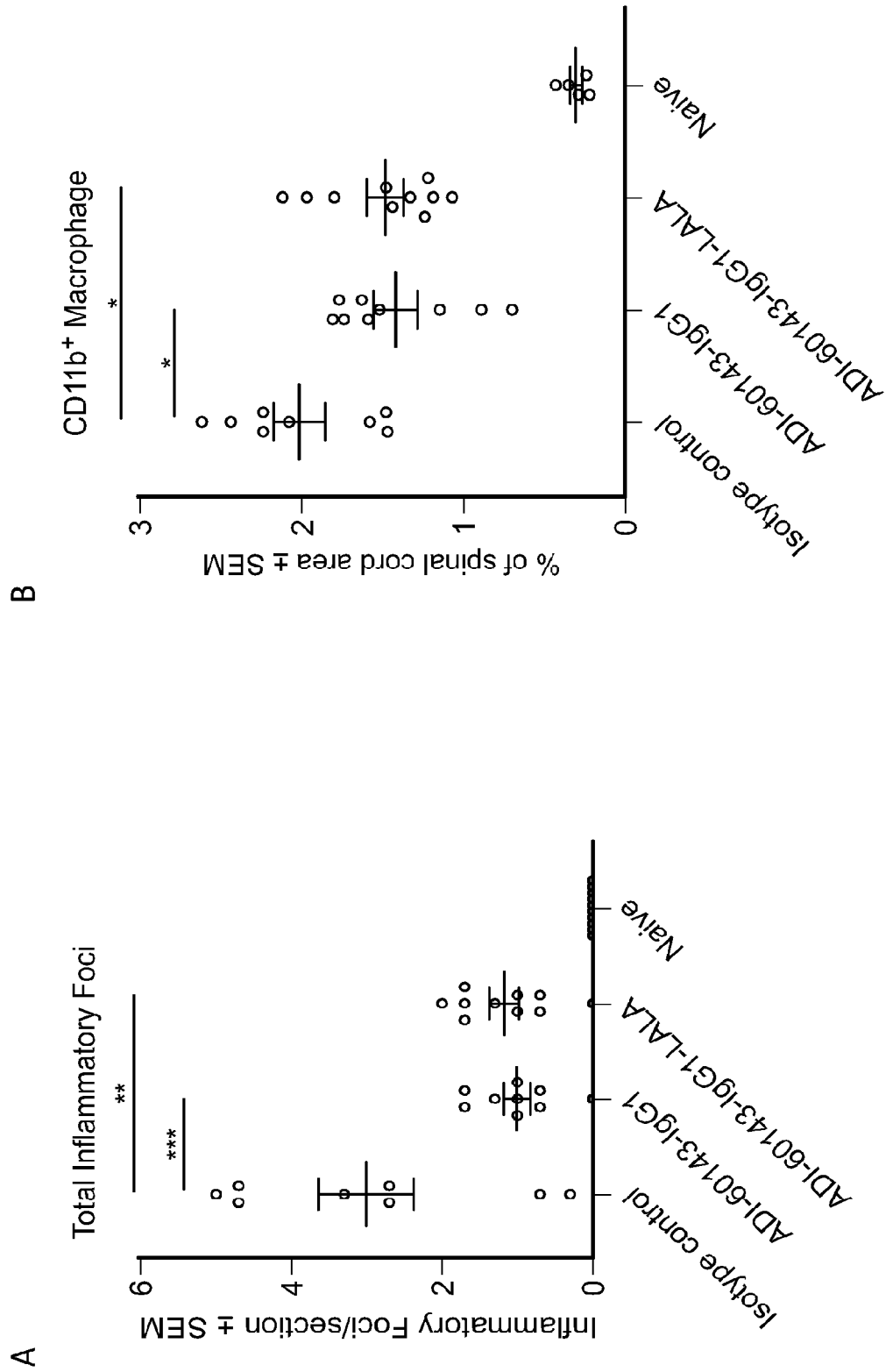


Figure 26

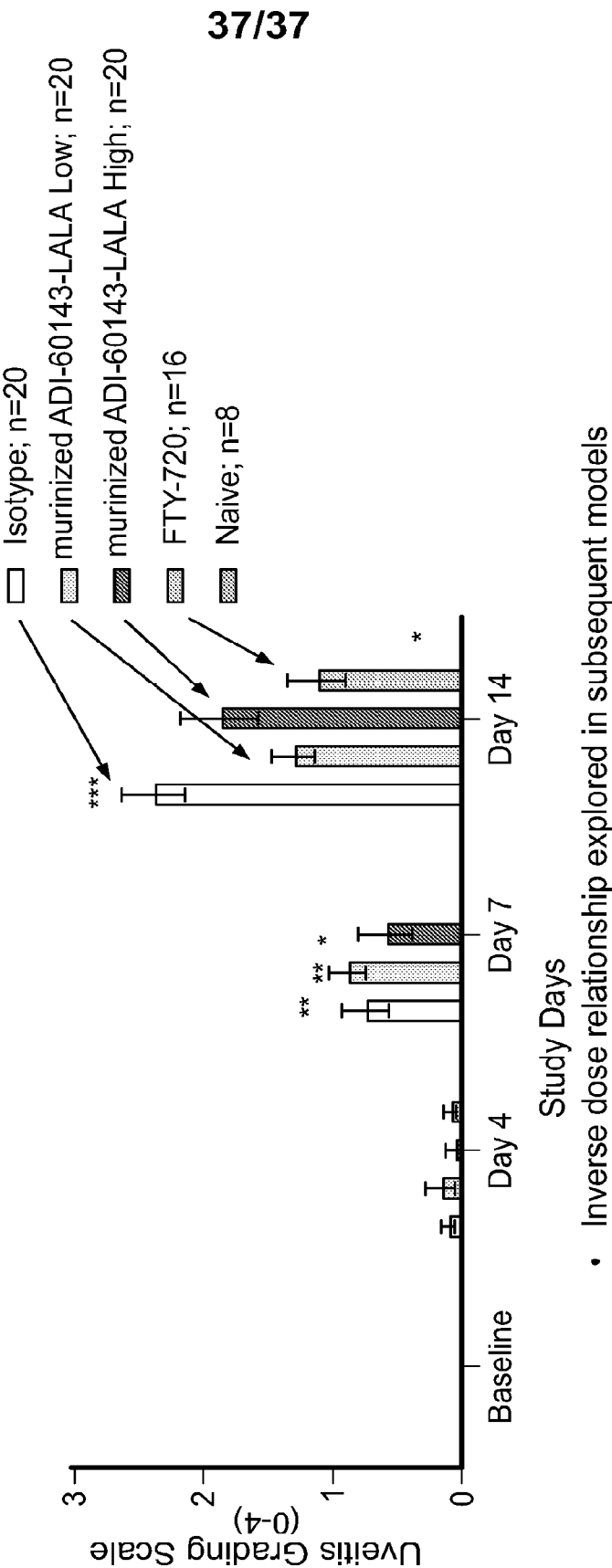


Figure 27

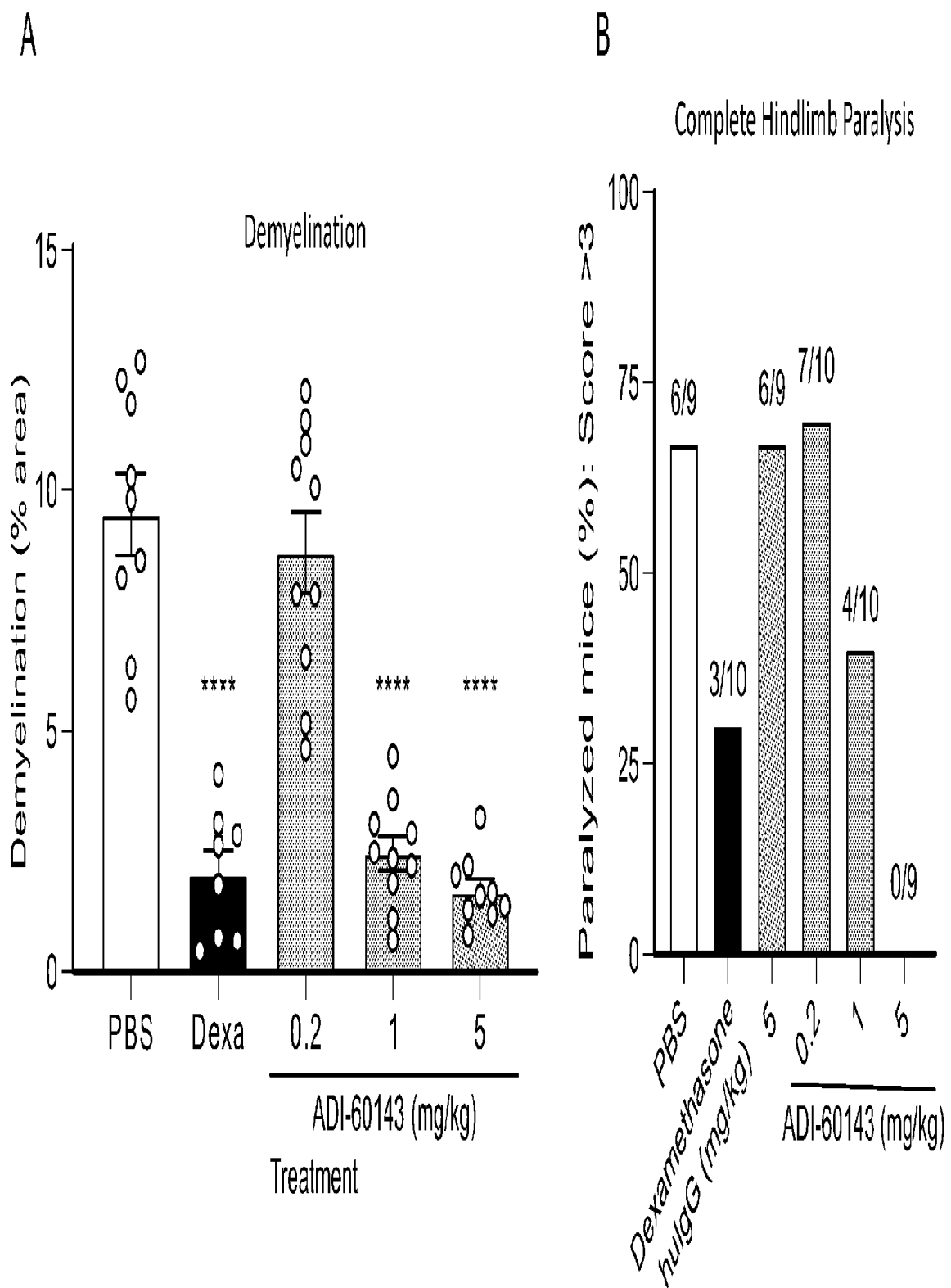


Figure 24